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THE UNIVERSITY OF ALBERTA

STEREOCHEMICAL STUDIES OF ACETYLCHOLINE AND RELATED COMPOUNDS

BY

© SHEN-CHUN HU

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
OF MASTER OF SCIENCE

FACULTY OF PHARMACY AND PHARMACEUTICAL SCIENCES

EDMONTON, ALBERTA

SPRING, 1970

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Stereochemical Studies of Acetylcholine and Related Compounds" submitted by Shen-Chou Wu in partial fulfilment of the requirements for the degree of Master of Science.

ABSTRACT

A review of the possible role of conformational isomerism in the physiological actions of acetylcholine (Ach) is given. A case is made for the further study of the conformation of Ach and that of analogs of greater molecular rigidity, and for the pharmacological evaluation of compounds of this type. To this end four synthetic series are described, namely,

a) some acylic Ach analogs in which one of the NMe groups is replaced by a bulkier alkyl or arylalkyl function,

b) (±)-*trans*- and *cis*-2-aminocyclohexyl acetate methiodides and related esters with potential anticholinergic properties,

c) analogs of the simple cyclohexane acetate methiodides containing an anchoring *t*-butyl substituent, and

d) some morpholine derivatives.

PMR characteristics of compounds synthesized are reported and interpreted in terms of configuration and conformation. These data, together with some IR dilution studies provide evidence for a preferred $\overset{+}{N}CCO$ gauche conformation for Ach and its analogs as solutes in water.

ACKNOWLEDGEMENTS

The author wishes to express his most sincere thanks to Dr. A.F. Casy for his able and enthusiastic supervision, instruction, and encouragement throughout the course of this work.

Special thanks are extended to Professor E.J. Ariëns of the Department of Pharmacology, University of Nijmegen, who kindly arranged the determination of the muscarinic and nicotinic activities of some compounds synthesized during the course of this investigation. To Dr. K.R. Kopecky, the author is indebted for his many useful discussions.

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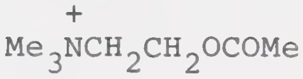
CHAPTER I

HISTORICAL INTRODUCTION

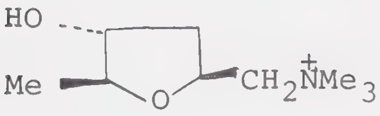
One of the functions of acetylcholine (Ach 1), is



$$Me_3\overset{+}{N}CH_2CH_2OCOMe$$

1

the transmission of nerve impulses between neuron and neuron, between neuron and muscle cell, and between neuron and secretory cell within the parasympathetic nervous system (Nachmansohn, 1959). Some of its actions in this respect are reproduced by (+)-muscarine (2) and others by nicotine (3), and these facts have given rise



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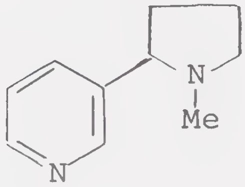
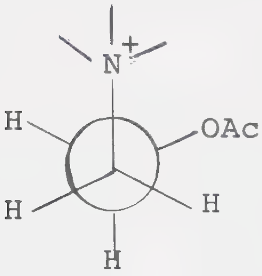


3

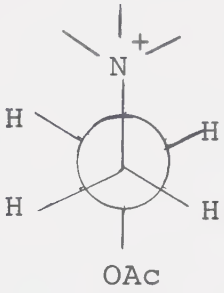
to the designation of Ach properties as either muscarinic or nicotinic. The former properties are blocked by atropine and the latter by hexamethonium.

The duality of action of Ach suggests the existence of at least two distinct types of Ach receptor and much speculation has been made regarding the possible role of conformational isomerism in the physiological action of Ach (Martin-Smith, *et al.*, 1967a). It may be

proposed, for example, that Ach in the gauche (or skewed) conformation (4a) associates at the muscarinic but not the nicotinic receptor, while the reverse is true for the trans conformer (4b). Conformational isomerism in

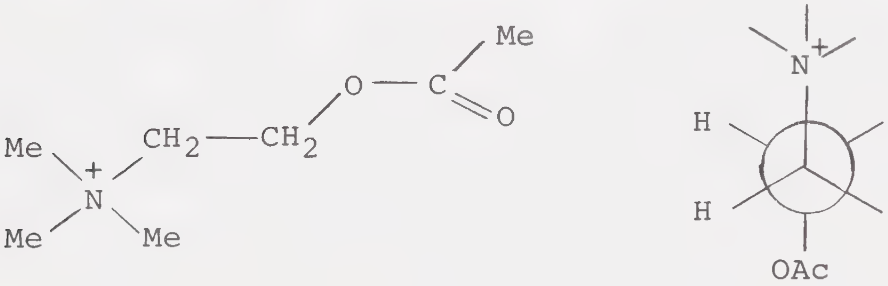


4a

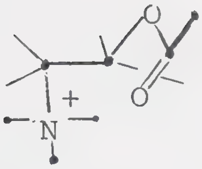


4b

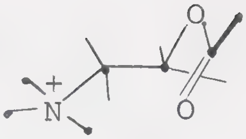
Ach depends upon free rotations about the C-C and C-O bonds of the choline fragment. An infinite number of conformers are possible and of these, nine separate well-defined conformations for Ach must be considered. These are the full staggered conformation (5) and four pairs of identical skewed forms (5a, 5b, 5c, and 5d) (Gill, 1965).



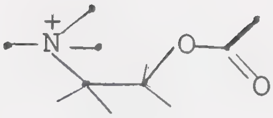
5



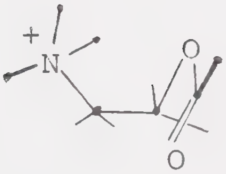
5a



5b



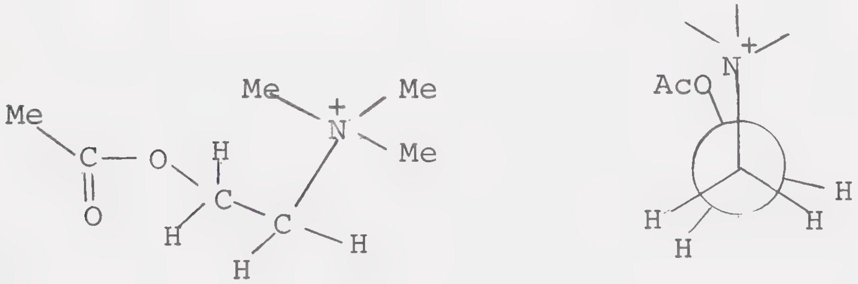
5c



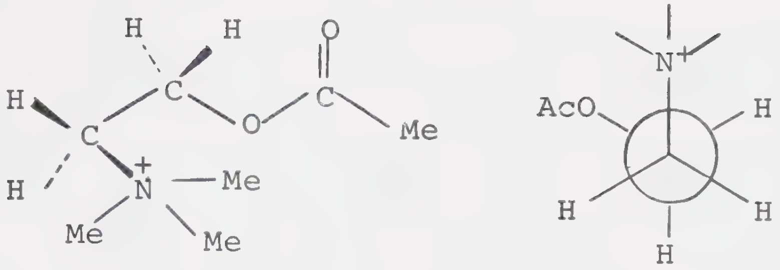
5d

Data of relevance to the problem of establishing the validity or otherwise of the conformational isomerism concept include 1) investigation of the preferred conformation of Ach under physiological condition, and 2) the pharmacological evaluation of rigid or semi-rigid Ach analogs which reproduce, in varying degree, gauche or trans conformation of Ach.

There is evidence from X-ray analyses (Canepa et al., 1966; Chothia and Pauling, 1968) and from a PMR study in deuterium oxide (Culvenor and Ham, 1966) that the preferred conformation (6 and 7) of Ach is that in which acyloxy oxygen is gauche to the nitrogen atom.



6 (from X-ray)

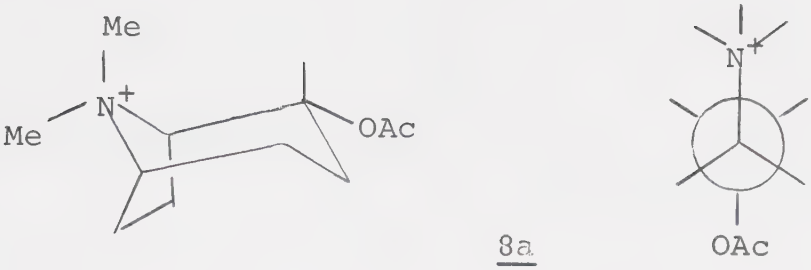


7 (from PMR)

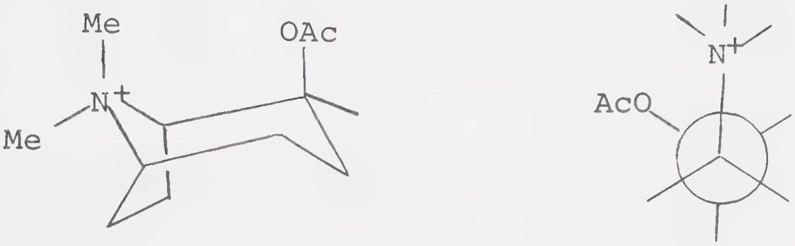
These reults are consistent with that deduced from molecular orbital calculations (Kier, 1967). On steric grounds, a trans arrangement is preferred, especially when the N and O functions are solvated, and the above-mentioned work indicates that some form of $\overset{+}{N}\cdots O$ interaction operates to offset steric hindrances. This view is supported by infrared studies in ethanol (Fellman and Fujita, 1962, 1963, 1965 and 1966), and by another work in water which has challenged the former's interpretation (Canepa and Mooney, 1965). Details of these spectroscopic studies are given later in the thesis.

Work upon more rigid analogs of Ach is summarized below:

a) Tropane Derivatives (Archer et al., 1962). 2α-Acetoxytropane methiodide (8a) (trans $\overset{+}{N}$/O geometry more probable) possesses weak muscarinic activity while 2β-acetoxytropane methiodide (8b) (gauche $\overset{+}{N}$/O more probable) possesses stronger nicotinic activity than the former. Muscarinic activity was absent in the β-isomer.

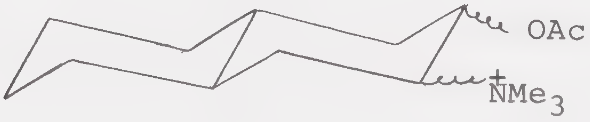


8a

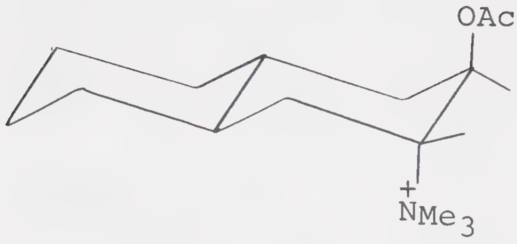


8b

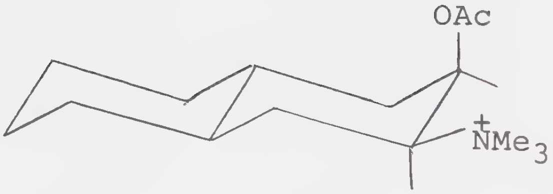
b) Decalin Derivatives (Smissman *et al.*, 1966; Smissman and Chappell, 1969). All four isomeric 3-trimethylammonium-2-acetoxy-*trans*-decalin iodides (9) have been tested as cholinergic agents on guinea pig ileum but are largely devoid of activity. The most potent one, (9a), (with formally axial $\overset{+}{N}$/axial OCOMe geometry) has a potency relative to Ach of 0.06. No



9



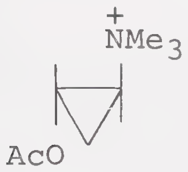
9a



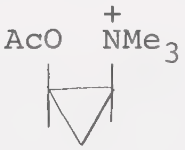
9b

nicotinic properties were found for (9a) and 3(e)-trimethylammonium-2(a)-acetoxy-*trans*-decalin iodide (9b).

c) Cyclopropane Derivatives (Armstrong *et al.*, 1968; Chiou *et al.*, 1969). *trans*- and *cis*-2-Acetoxycyclopropyl-trimethylammonium iodides (ACTM, 10a and 10b)



10a

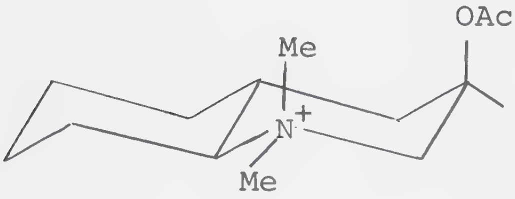


10b

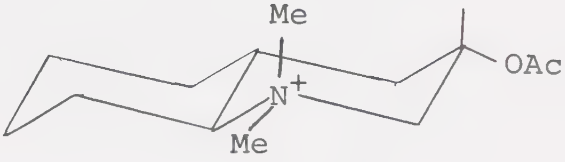
were prepared and tested for both muscarinic and nicotinic activities. The (+)-*trans*-ACTM was found to have strong muscarinic activities on dog blood pressure (4.7 times more active than Ach) and guinea pig ileum (1.13 times of Ach), while the levo form was only feebly active in these respects. The (+)- and (-)-*cis*-ACTM were devoid of muscarinic activities and

were expected to have strong nicotinic activities owing to their cisoid conformation, however, negligible nicotinic activity on frog rectus abdominis muscle was observed.

d) Decahydroquinoline Derivatives (Smissman and Chappell, 1969). In an assay of muscarinic action, 1-methyl-3(a)-acetoxy-trans-decahydroquinoline methiodide (11a) proved to be a partial agonist having a relative potency on



11a



11b

a molar basis of 0.02 as compared to Ach. The equatorial isomer (11b) had no agonist properties. Neither of the isomers were found to be active as nicotinic agents.

The cited reports, therefore, strongly suggest that the transoid conformation of $\overset{+}{N}/O$ favors action on the muscarinic receptor, although all cyclic analogs of Ach tested, except the cyclopropane derivatives, are not really conformationally rigid molecules and deformation of the cyclic rings are probable owing to the steric repulsion between the cationic nitrogen head or acetoxy group and the rest of the molecule.

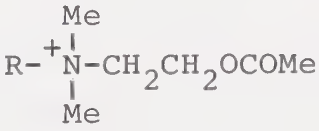
CHAPTER II

AIMS AND OBJECTS

It is evident from the preceding literature survey that clear-cut evidence of the conformational requirements of the reported muscarinic and nicotinic agonists remains to be solved. In an attempt to provide further information about the interactions between cholinergic agonists and their receptors, the present work was planned.

1) To extend the spectroscopic studies (PMR and IR) of Ach with a view to the firm establishment of the preferred conformation of this molecule, especially under conditions close to the physiological environment, and to gain a better understanding of interactions (steric and electronic) which govern molecular configuration in this compound.

This work involved a) the synthesis of Ach analogs of type (12) in which one of the NMe group of Ach is replaced by a bulky alkyl or arylalkyl group and b) the synthesis of certain morpholine derivatives to serve as possible models for the PMR analyses.



$$R-\overset{+}{N}(Me)_2-CH_2CH_2OCOMe$$

12

2) To extend knowledge of more rigid analogs of Ach. This work involved the stereochemical assignments (configurational and conformational) and pharmacological evaluation of two series of Ach analogs based upon cyclohexane. These were

a) (±)-trans- and cis-2-dimethylaminocyclohexyl acetate methiodides.

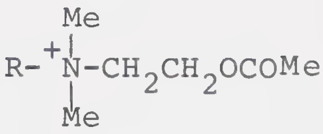
b) analogs of the above containing an anchoring t-butyl substituent. These compounds were considered for study in the hope that some would display potencies higher than that obtained in the related decalin derivatives of Smissman and others (1966) and allow a conclusive identification of the conformational requirements of the muscarinic and nicotinic receptors. The synthesis of a few potential antagonist analogs was planned in addition to agonists.

CHAPTER III

DISCUSSION OF EXPERIMENTAL RESULTS

i) SYNTHESIS OF ACYCLIC ACETYLCHOLINE ANALOGS

Acyclic Ach analogs (13-16) of type (12) could not



$$R-\overset{+}{N}(Me)_2-CH_2CH_2OCOMe$$

12

R = $-CH_2CH{=}CH_2$	13
$-CH_2Ph$	14
$-CHMe_2$	15
-*t*-Bu	16

be traced in the literature. At first, 2-dimethylaminoethyl acetate (17) was used as substrate for quaternization with various alkyl halides. The allyl derivative

$$Me_2NCH_2CH_2OCOMe$$

17

(13) was synthesized by this route, but difficulties were encountered during the preparation of the benzyl and isopropyl analogs (14 and 15) (see later). 2-Dimethylaminoethanol was thus used as the starting material in these cases. As regards to the *t*-butyl analog (16), reaction of

the ester (17) with t-butyl bromide gave the hydrobromide of the ester (17) instead of the expected quaternary salt (16). This compound was subsequently synthesized from 2-t-butylaminoethanol (18).

$$t\text{-Bu-NHCH}_2\text{CH}_2\text{OH}$$

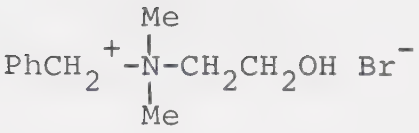
18

(β-Acetoxyethyl)allyldimethylammonium Bromide (13)

Allyl bromide in acetone and 2-dimethylaminoethyl acetate in acetone were mixed and spontaneously gave the desired product (13) in quantitative yield.

(β-Acetoxyethyl)benzyldimethylammonium Bromide (14)

An acetone solution of benzyl bromide and 2-dimethylaminoethyl acetate was heated under reflux for three hours. The IR spectrum of crystals after removal of the reaction mixture showed a strong ν_{OH} band at 3300 cm^{-1} and a relatively weak $\nu_{C=O}$ band at 1745 cm^{-1}. Further recrystallization gave the pure benzyldimethyl (β-hydroxyethyl)ammonium bromide (19); the m.p. of the product was not depressed by mixing with the compound which resulted from quaternization of 2-dimethylaminoethanol with benzyl bromide. The title compound was prepared by quaternizing 2-dimethylaminoethanol with benzyl



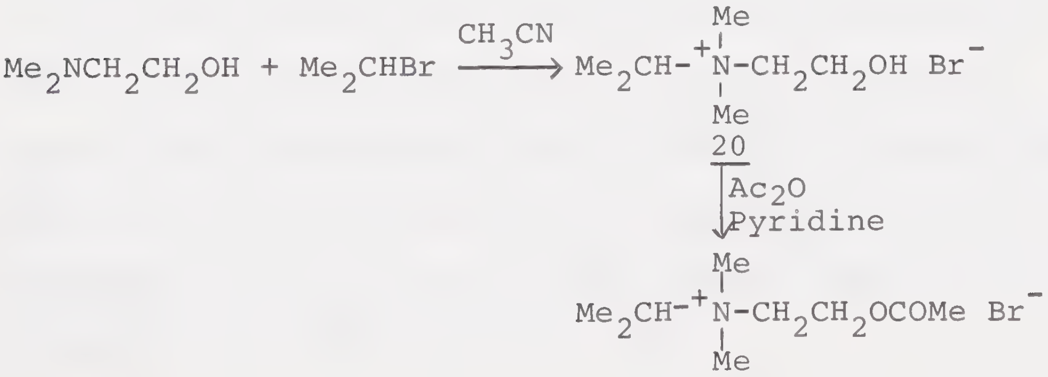
$$PhCH_2\overset{+}{-}\underset{Me}{\overset{Me}{N}}-CH_2CH_2OH\ Br^-$$

19

bromide and then by acetylating the resultant quaternary salt (19) with acetic anhydride in pyridine.

(β-Acetoxyethyl)dimethylisopropylammonium Bromide (15)

The preparation of the title compound was attempted several times by refluxing an acetone solution of isopropyl bromide and 2-dimethylaminoethyl acetate for a period of 2 hours to 24 hours, however, no crystals were obtained or the yield was poor. When acetonitrile was used as solvent, the desired product, about 10% yield, was isolated after a 24 hours reflux period or by leaving for 7 days at room temperature. This route was not promising and the method used for making benzyl analog (14) was employed as illustrated in the following scheme:



$$Me_2NCH_2CH_2OH + Me_2CHBr \xrightarrow{CH_3CN} Me_2CH\overset{+}{-}\underset{Me}{\overset{Me}{N}}-CH_2CH_2OH\ Br^-$$

20

$$\downarrow Ac_2O,\ Pyridine$$

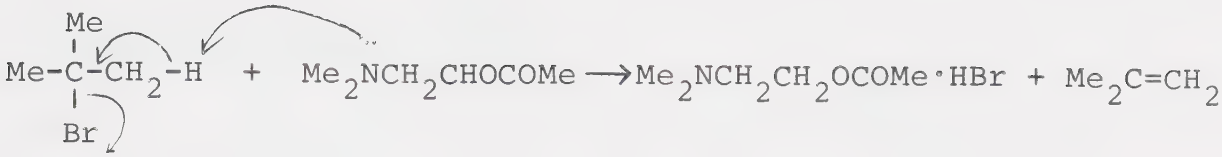
$$Me_2CH\overset{+}{-}\underset{Me}{\overset{Me}{N}}-CH_2CH_2OCOMe\ Br^-$$

15

It was found that acetonitrile was a better reaction solvent than acetone for preparing the alcohol quaternary salt (20). The reason for this is probably due to a difference in the dielectric constants of the two solvents, that of the former being the higher, since solvent polarity plays an important role in reactions in which ions are generated. The title compound easily undergoes hydrolysis.

(β-Acetoxyethyl)-t-butyldimethylammonium Iodide (16)

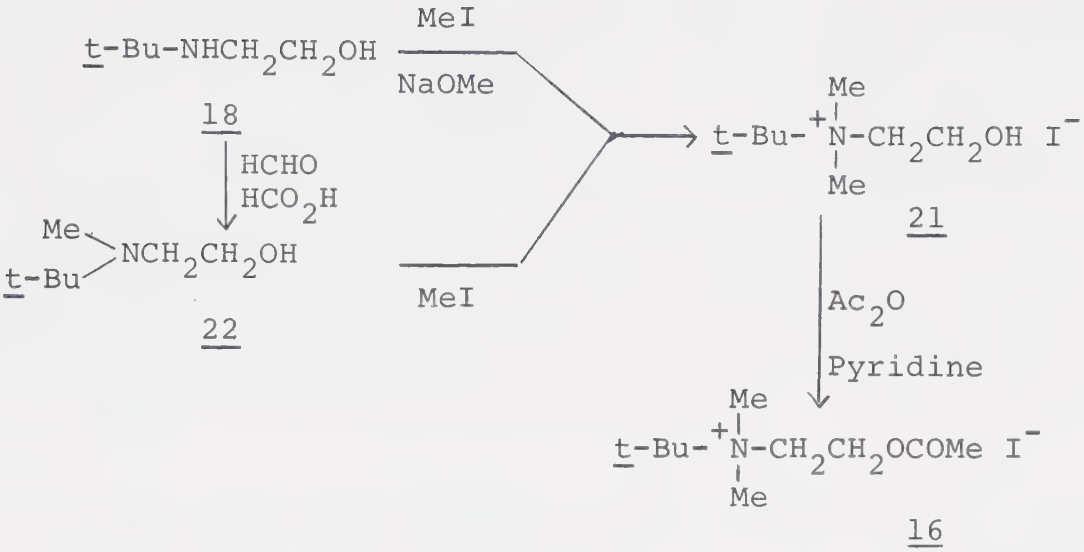
Various reaction conditions, such as refluxing the acetonitrile solution of 2-dimethylaminoethyl acetate and t-butyl bromide for 5 to 80 hours, or standing the solution at room temperature were tried to obtain the title compound. It was found that the product isolated was the hydrobromide of 2-dimethylaminoethyl acetate, the m.p. of which agreed with the literature value (Tammelin, 1957). The elemental analysis of this salt also supported the designed formula. The mechanism for the formation of the hydrobromide salt instead of t-butyl quaternary salt (16) is that elimination of t-butyl bromide is favored over nucleophilic substitution of 2-dimethylaminoethyl acetate by t-butyl bromide, since the reactivity of carbonium ion in S_N reaction decreases in order $1^{o}>2^{o}>3^{o}$. A probable mechanism is shown below:

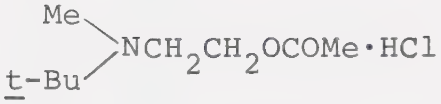


$$Me-\underset{Br}{\overset{Me}{C}}-CH_2-H \quad + \quad Me_2NCH_2CHOCOMe \longrightarrow Me_2NCH_2CH_2OCOMe\cdot HBr \; + \; Me_2C{=}CH_2$$

The starting material used in the present work was commercially available 2-*t*-butylaminoethanol (18). One step of N-methylation and further quaternization of 2-*t*-butylaminoethanol with methyl iodide in the presence of sodium methoxide gave *t*-butyldimethylamino-(β-hydroxyethyl)ammonium iodide (21), which was also prepared by quaternization of 2-(N-t-butyl-N-methylamino)-ethanol (22) obtained from N-methylation of (18) by Leukart's procedure. The alcohol quaternary salt (21) was then acetylated with acetic anhydride in pyridine to afford the title compound (the synthetic pathway is given below). This compound is easy to hydrolyze and the reason for this hydrolysis is probably due to the presence of the positive nitrogen head. To avoid hydrolysis during the recrystallization process, the product was dissolved in ethanol without heat and the crystals collected as soon as formed.

2-(N-*t*-Butyl-N-methylamino)ethyl acetate hydrochloride (23) was made by heating the hydrochloride of (22) with acetic anhydride. The compound (23) is also easy to hydrolyze.





23

2-Dimethylamino-1-methylethyl Acetate (24) and Its Derivatives

Acetylation of 2-dimethylamino-1-methylethyl alcohol with acetic anhydride or acetyl chloride produced the title compound. Its hydrobromide (25) was made by treatment of the free base (24) with hydrogen bromide.

$Me_2NCH_2CH(Me)OCOMe$

24

$Me_2CH_2CH(Me)OCOMe \cdot HBr$

25

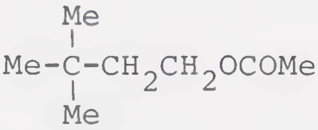
2-Aminoethyl Acetate Hydrochloride (26)

$H_2NCH_2CH_2OCOMe \cdot HCl$

26

The reported method that a mixture of 2-aminoethanol and acetic acid saturated with hydrogen chloride at 0°C gives the title compound (Crane and Rydon, 1947) was attempted but the product isolated was the hydrochloride of 2-aminoethanol. Acetylation of the hydrochloride of 2-aminoethanol in acetone using acetic anhydride provided the desired product (26) (Hansen, 1963).

3,3-Dimethyl-*n*-butyl Acetate (27)



$$\mathrm{Me{-}\overset{\overset{\large Me}{|}}{\underset{\underset{\large Me}{|}}{C}}{-}CH_2CH_2OCOMe}$$

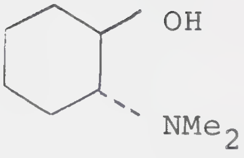
27

A mixture of 3,3-Dimethyl-*n*-butanol (commercially available) and acetic anhydride was refluxed to yield the title compound (Burgen, 1965).

ii) (A) SYNTHESIS OF SIMPLE CYCLOHEXANE ACETYLCHOLINE ANALOGS

Isomeric 2-Dimethylaminocyclohexyl Acetate Methiodides

In the literature (Baldridge *et al.*, 1955; Adank and Stoll, 1959), (±)-*trans*-2-dimethylaminocyclohexanol (28) and its *cis* isomer (29) have been reported as intermediates for making (±)-*trans*-2-dimethylaminocyclohexyl



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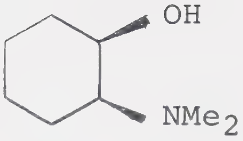
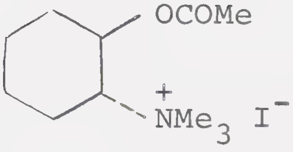


29

acetate methiodide (30) and its *cis* isomer (31). The



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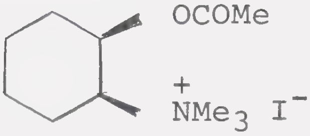

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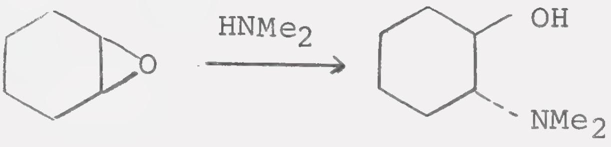
trans isomer (28) was made by treating cyclohexene oxide with dimethylamine; ring-opening reactions of this type are known

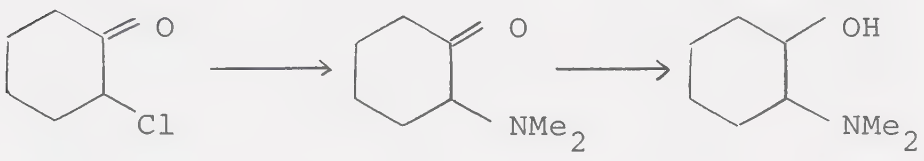


28

to follow a *trans* diaxial pathway (Barton and Cookson, 1956; Parker and Isaacs, 1959). After acetylation and quaternization with methyl iodide, the compound (28) gave (±)-*trans*-2-dimethylaminocyclohexyl acetate methiodide (30).

Two routes have been reported for the synthesis of the corresponding *cis* isomer (29). In one, 2-chlorocyclohexanone (32) and

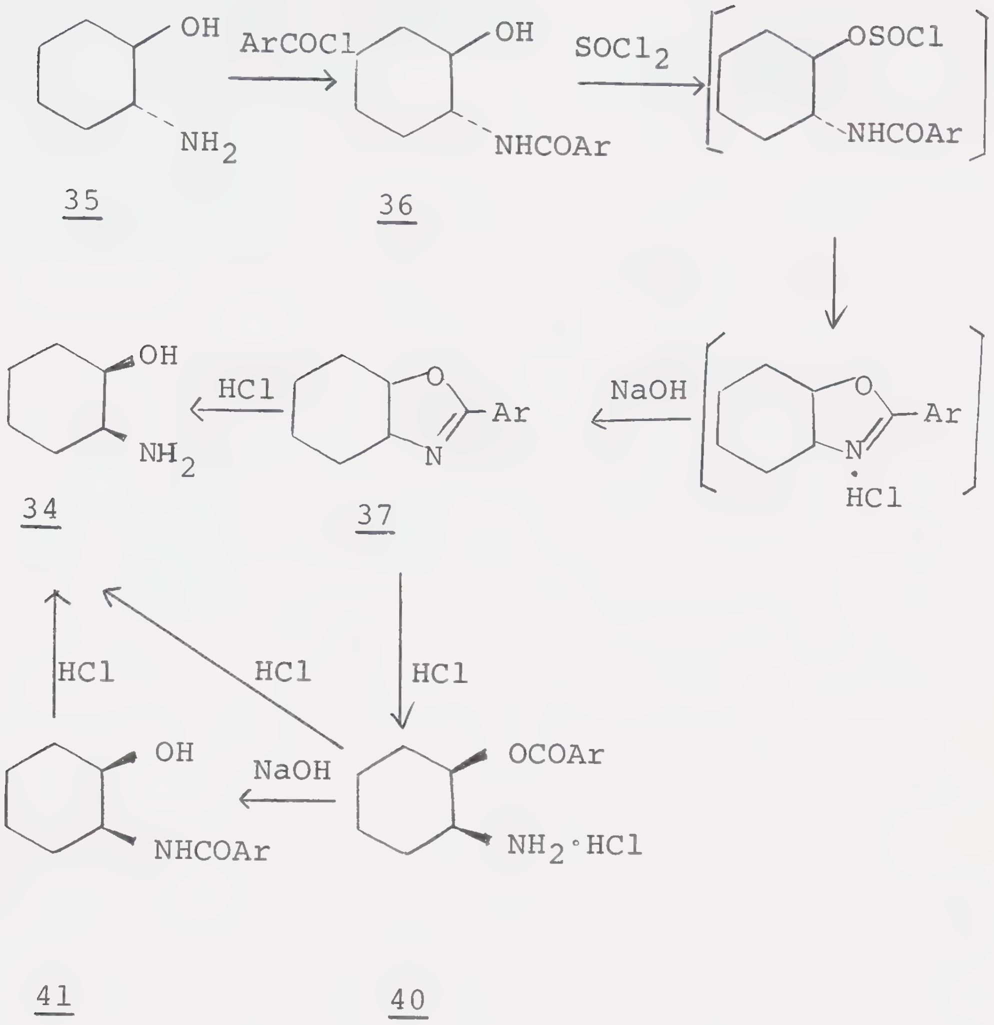
dimethylamine were heated under pressure and the resultant aminoketone (33), without distillation or purification, was catalytically reduced to give the *cis*-dimethylaminocyclohexanol (29). The product (29) was identical with the aminoalcohol derived from 2-acetamidophenol (see below) and was assumed to have a *cis* configuration (Mousseron *et al*., 1950).



32 33 29

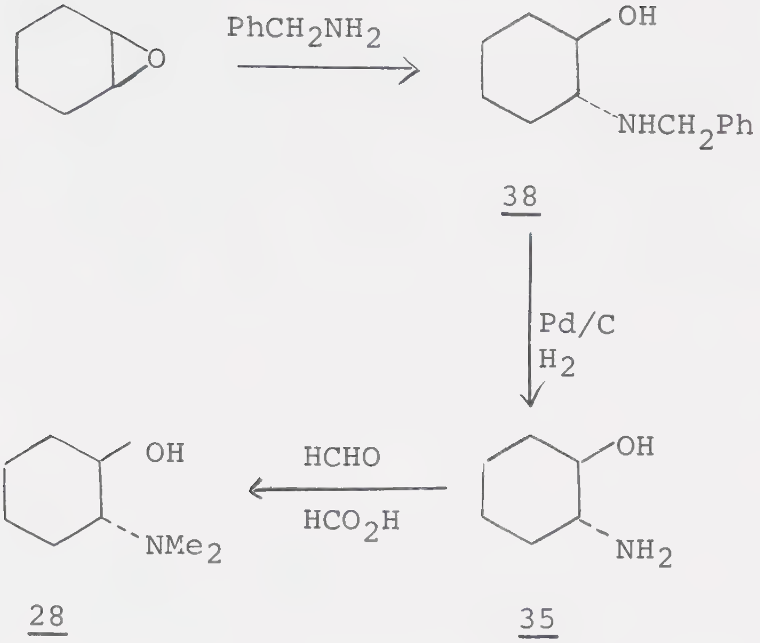
In the second route, (±)-*cis*-2-dimethylaminocyclohexanol (29) was prepared by N, N-dimethylation of (±)-*cis*-2-aminocyclohexanol (34) with methyl tosylate (Taguchi *et al*., 1963). The latter (34) has been synthesized by the hydrogenation of 2-acetaminophenol with Raney nickel followed by hydrolysis (McCasland *et al*., 1949), and by the conversion of (±)-*trans*-2-aminocyclohexanol (35) via its *p*-nitrobenzamide (36) to (±)-2-*p*-nitrophenyl-4,5-*cis*-cyclohexanoöxazoline-2 (37) and the subsequent hydrolysis of the product thus formed (McCasland and Smith, 1950). The latter route is illustrated in the following scheme;

note that displacement of the chlorosulfonyl group (OSOCl) is an inversion reaction.



Ar- = $-Ph-NO_2-$p

In the present work the synthesis of (±)-trans-2-dimethylaminocyclohexanol (28) was based on the reaction of cyclohexene oxide with benzylamine. This route was chosen because a) it avoided the necessity of employing



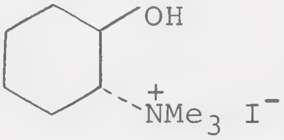
a pressure reaction, and b) the resultant primary amine (35), (±)-*trans*-2-aminocyclohexanol, involved as an intermediate, was capable of being transformed into its *cis* epimer (34). Winternitz and Thakkar (1952) carried out the reaction of cyclohexene oxide and benzylamine under pressure, but it was found, in this work, that the reaction proceeded well under reflux conditions at atmospheric pressure in the presence of water. (PMR data supporting the *trans* opening will be discussed later). The *trans* aminoalcohol (35) formed by catalytic debenzylation of (38) was then N,N-dimethylated by using Leukart's procedure (formaldehyde and formic acid), and the resultant

tertiary amine (28) acetylated and then quaternized with methyl iodide to give (±)-trans-2-dimethylaminocyclohexyl acetate methiodide (30).

Reported melting point data for the trans acetate methiodide (30) lack consistency (shown below), and the m.p. of the product presently obtained fell between two of these values. The elemental analysis of this material

		m.p.
Baldridge et al.	(1955)	210-211° (monohydrate)
Adank and Stoll	(1959)	134-135°
Kay and Robinson	(1969)	161-165°
Present work		148-149°

was consistent with anhydrous material; its m.p. was 145-49° when recrystallized from ethanol-ether containing two drops of water (a higher m.p. has been claimed for the monohydrate). Its IR spectrum showed a characteristic absorption band at 1730 cm^{-1} (due to the ester group), but in addition a medium band at 3490 cm^{-1} with a shoulder was also present. From the analytical results this band is unlikely to be due to the water of crystallization and the absence of the free alcohol methiodide (39),



39

(±)-trans-2-dimethylaminocyclohexanol methiodide, was established by recording an IR spectrum of a mixture of the alcohol methiodide (39) and its acetate (30) when a peak due to the hydroxyl stretching vibration appeared at 3200 cm^{-1} (see Figure 1). It is possible that the band at 3490 cm^{-1} is an unusually strong overtone of the ester group which absorbs at 1730 cm^{-1} (Williams and Fleming, 1966). This type of overtone of the ester group was also seen in the corresponding cis isomer (31) (this will be mentioned below) and some cyclic analogs (mentioned in the experimental).

(±)-cis-2-Aminocyclohexanol (34) was derived from its trans isomer (35) by treating its p-nitrobenzamide (36) with thionyl chloride (McCasland and Smith, 1950) and gave the corresponding acetate methiodide (31) by the same procedure as described for making its trans isomer (30). The product (31) had a melting point corresponding with literature values (Baldridge et al., 1955; Adank and Stoll, 1959; Kay and Robinson, 1969). A medium band at 3450 cm^{-1} with a shoulder appeared in its IR spectrum. This was similar to the band seen in the spectrum of the trans isomer (30) and may, as before, be attributed to an overtone of the ester group absorbing at 1735 cm^{-1}.

In all cases (±)-cis-2-aminocyclohexyl p-nitrobenzoate hydrochloride (40) resulted in addition to the oxazoline (37) during the preparation of the cis oxazoline (37) when (±)-

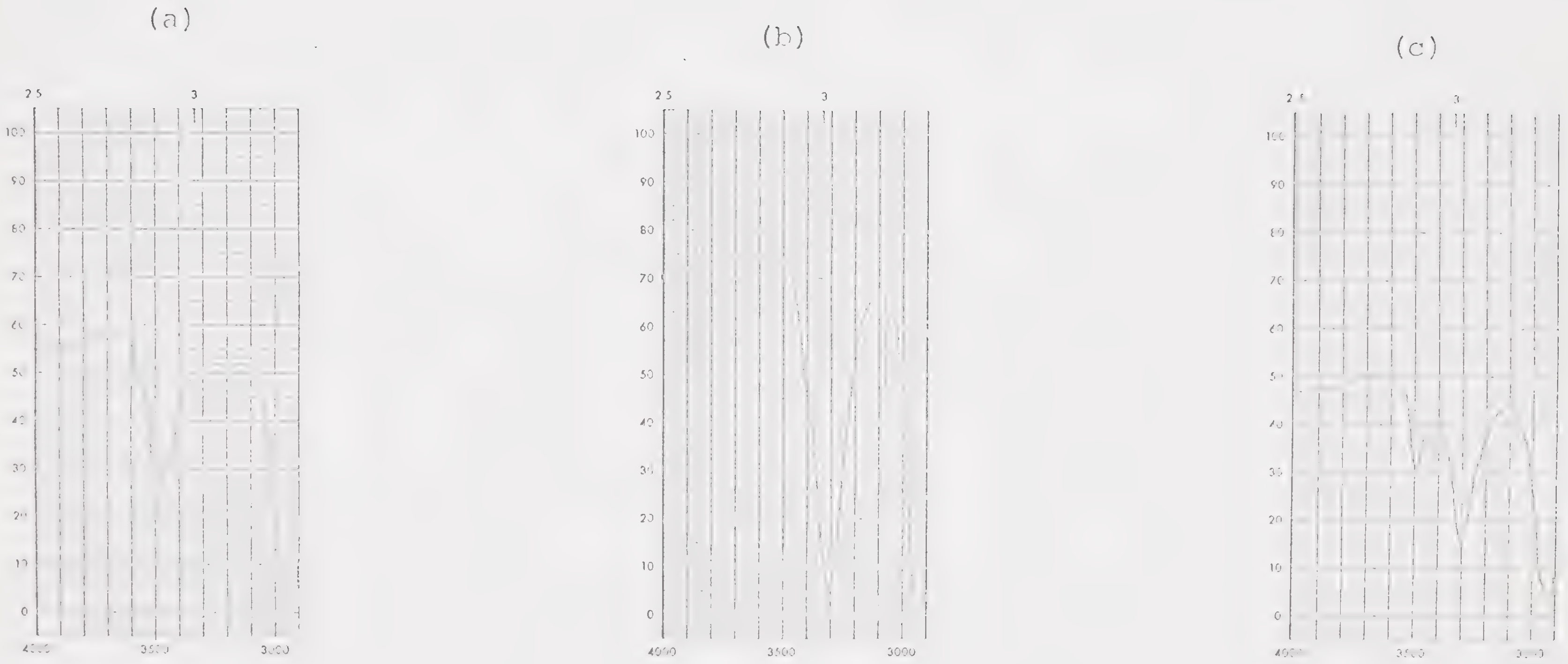


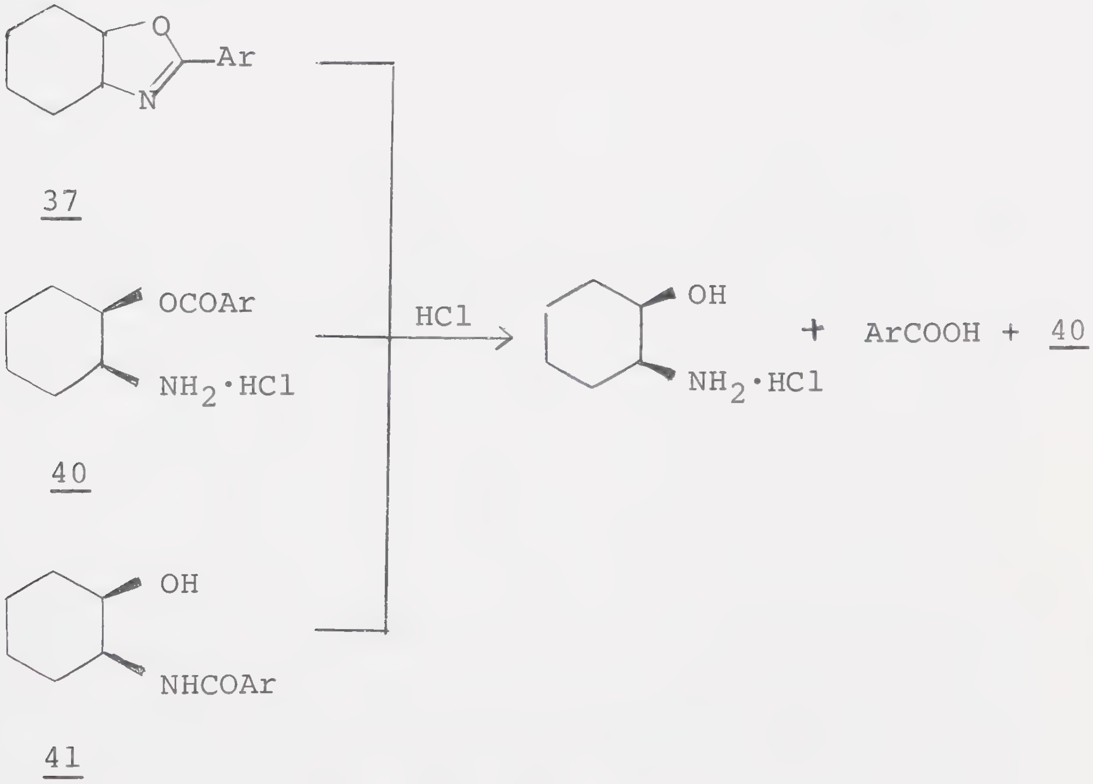
FIGURE 1. Part of the IR spectra of (±)-trans-2-dimethylaminocyclohexyl acetate methiodide (a), (±)-trans-2-dimethylaminocyclohexanol methiodide (b) and a prepared mixture of (±)-trans-2-dimethylaminocyclohexyl acetate methiodide and (±)-trans-2-dimethylaminocyclohexanol methiodide (c). Recorded on Beckman IR-10 as Nujol mulls.

trans-2-*p*-nitrobenzamidocyclohexanol was treated with thionyl chloride. Hydrochloric acid was generated during this reaction and also during the washing procedure, and this reagent is known to effect hydrolysis of oxazolines.

The stereochemistry of reactions involved in the formation and the ring opening of oxazolines has been established, and the assignment of the *cis* configuration to the thus formed oxazoline and the *cis*-2-aminocyclohexanol (**34**) derived from the oxazoline was based on this knowledge (Winstein and Boschan, 1950). PMR evidence of the *cis* configuration of the aminoalcohol (**34**) will be described later.

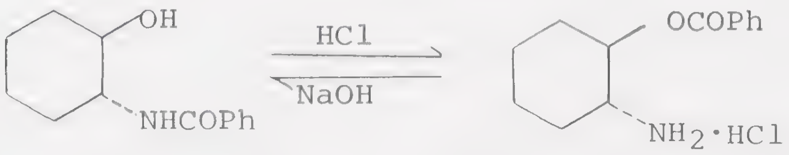
Treatment of 2-*p*-nitrophenyl-4,5-*cis*-cyclohexanoöxazoline-2 (**37**) with $HCl-H_2O$ (10 min. reflux) gave the corresponding *cis* aminoester hydrochloride (**40**), which by O → N acyl migration rearranged to (±)-2-*p*-nitrobenzamidocyclohexanol (**41**) upon treatment with base. Acidic hydrolysis of the oxazoline (**37**), the aminoester hydrochloride (**40**), or the benzamide (**41**) eventually yielded the (±)-*cis*-2-aminocyclohexanol (**34**), but this step presented difficulties not anticipated from the literature report (McCasland and Smith, 1950). It is claimed that the *cis* aminoalcohol (**34**) is obtained in high yield (73-75%) by refluxing the compounds (**37**, **40** and **41**) in 4 N hydrochloric acid for 3-4 hours This procedure was repeated several times and the yield obtained from each substrate was consistently low (about

20% or below), even when the reflux period was prolonged to 48 hours. In all cases, the hydrolysis product was a mixture of the *cis* aminoester hydrochloride (40) (the benzamide derivative was converted to the compound (40) by N → O acyl migration explained in the following paragraph), *p*-nitrobenzoic acid and the desired aminoalcohol (34) hydrochloride. The last salt was present in the filtrate obtained after filtration of the cold reaction product. The IR spectrum of the residue was identical with that of a prepared mixture of the aminoester HCl (40) and *p*-nitrobenzoic acid (details in the experimental).

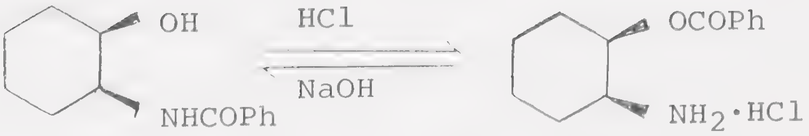


Ar- = -*p*-NO_2-Ph

Fodor and Kiss (1950) reported that (±)-*trans* and *cis*-2-benzamidocyclohexanol (42 and 43) underwent N → O acyl migration to the corresponding aminoester hydrochlorides (44 and 45) when heated with ethanolic hydrochloric acid in a sealed tube. The N → O acyl migrated compounds (44 and 45) upon treatment with base were reconverted to the original compounds (42 and 43) by O → N acyl migration.



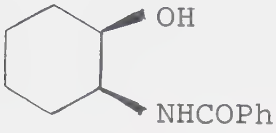
42 44



43 45

N → O acyl migration also occured when the *cis* benzamide (43) was heated under reflux with 4N aqueous hydrochloric acid for 11 hours (Fodor and Kiss, 1950, heated 43 with HCl in a sealed tube for 2 hours), as was clearly evident

from IR data upon the compound (43) and (45) (see below).



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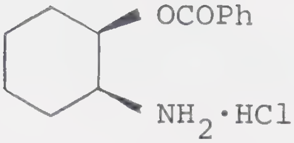


45

$\nu_{C=O}$ (amide) = 1625 cm^{-1}

ν_{OH} = 3320 and 3270 cm^{-1}

$\nu_{C=O}$ (ester) = 1725 cm^{-1}

$\nu_{\overset{+}{N}H_3}$ = 2700-2450 cm^{-1}

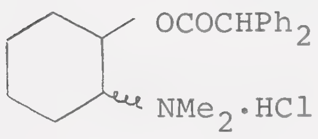
The cold reaction mixture was filtered, the residue being identified as benzoic acid. The filtrate was concentrated and cooled, and the aminoester hydrochloride (45) separated out as the first crop.

In an attempt to improve the yield of (±)-*cis*-2-aminocyclohexanol (34), hydrolysis of aminoester HCl (40) and the nitrobenzamide (41) under alkaline condition was investigated. Aqueous potassium hydroxide had no effect upon the nitrobenzamide derivative but 5% alcoholic potassium hydroxide proved very effective and gave high yield (above 90%) of the *cis* aminoalcohol for both substrates (40 and 41).

Isomeric 2-Dimethylaminocyclohexyl Diphenylacetate Hydrochlorides and Methiodides

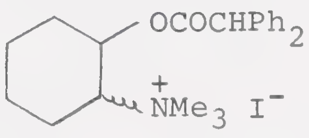
These title compounds have been made before, but

their physical data were not given (Friess *et al.*, 1958). The route used for making these compounds was analogous to that described previously for (±)-trans- and *cis*-2-dimethylaminocyclohexyl acetate methiodides (**30** and **31**). Reaction of diphenylacetic acid and thionyl chloride gave diphenylacetyl chloride (**46**) from which (±)-*trans* and *cis*-2-dimethylaminocyclohexyl diphenylacetate hydrochlorides (**47** and **48**) resulted after its treatment with the corresponding dimethylaminoalcohols (**28** and **29**). The hydrochlorides were made basic with ammonia and the free bases quaternized with methyl iodide to produce the corresponding methiodides (**49** and **50**).



47 (*trans*)

48 (*cis*)



49 (*trans*)

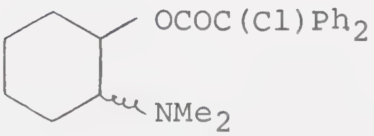
50 (*cis*)

Recrystallization of the methiodides (**49** and **50**) proved difficult; crystals did not separate readily from ethanol-ether and hydrolysis occurred if the solution was left in the refrigerator too long. This difficulty was

overcome by using an ethanol-ethyl acetate-ether mixture as crystallization solvent.

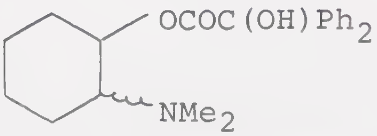
Isomeric 2-Dimethylaminocyclohexyl Benzilate Hydrochlorides and Methiodides

The reported method (Adank and Stoll, 1959) for making (±)-*trans*- and *cis*-2-dimethylaminocyclohexyl benzilates (51 and 52) is the hydrolysis of (±)-*trans*- and *cis*-2-dimethylaminocyclohexyl diphenylchloroacetates (53 and 54) in water, the latter being derived from 2-dimethylaminoalcohols (28 and 29) and diphenylchloroacetyl chloride.



53 (*trans*)

54 (*cis*)

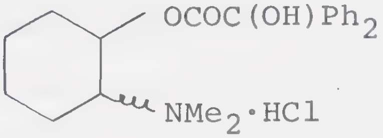


51 (*trans*)

52 (*cis*)

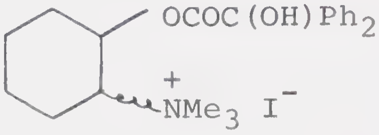
The esters (51 and 52) presently obtained were prepared by transesterification of the dimethylaminoalcohols (28 and 29) in the presence of sodium methoxide with methyl benzilate (Cannon, 1960), an ester which is commercially available. The yield was almost quantitative.

Treatment of the esters thus formed with ethanol saturated with hydrogen chloride or with methyl iodide gave the corresponding hydrochlorides (55 and 56) or methiodides (57 and 58).



55 (trans)

56 (cis)



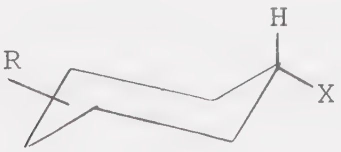
57 (trans)

58 (cis)

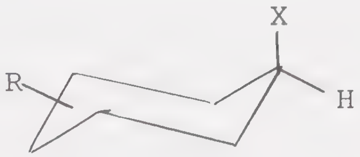
ii) (B) PMR EVIDENCE OF CONFIGURATION AND CONFORMATION OF ISOMERIC 2-AMINOCYCLOHEXANOLS AND THEIR DERIVATIVES

Principles

Stereochemical information about cyclohexane derivatives of the type (59a) and (59b) may be obtained



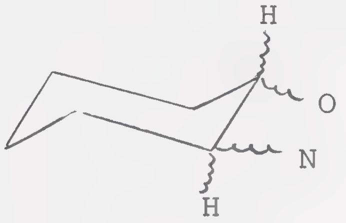
59a



59b

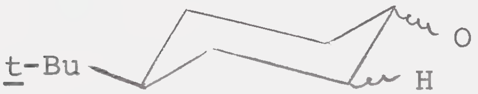
from the PMR characteristics of the methine proton. In the first case, the signal of the axial proton in (59a) is generally higher than that of the equatorial proton in (59b) as a result of long range shielding effects associated with carbon-carbon single bonds that bear a 2,3 relationship to the proton in question (Jackman, 1959; ApSimon *et al.*, 1967). Secondly, the equatorial signal will show less extensive spin-spin coupling with vicinal neighbours than the axial signal as a result of the dihedral angle (ϕ) dependence of coupling constants (Karplus, 1959, 1960). In 59a, two axial-axial ($\phi = 180^{\circ}$) and two axial-equatorial ($\phi = 60^{\circ}$) couplings will operate, whereas in 59b, two equatorial-axial ($\phi = 60^{\circ}$) and two equatorial-equatorial ($\phi = 60^{\circ}$). In cyclohexane rings J_{aa} usually falls in the range 8-14 Hz whereas a/e and e/e couplings have significantly smaller values in the range 0-6 Hz (Thomas, 1968). As a result the axial methine signal will be broader than the equatorial resonance and, if resolved, will display typical J_{aa} and J_{ae} coupling constants. Methine signals often may not be analysed and in such cases features of value are the signal base width or width at half height (W_H). Long range couplings also contribute to signal width so absolute values may be deceptive. Comparative values of signal width between the methine signals of isomers may, however, be significant and allow their differentiation.

In the present series (60), two methine signals are involved and must be identified. This has been found usually possible on the basis of relative field position (the resonance of the proton attached to the more electronegative atom, oxygen, should fall at lower field), and upon use of O- and N-acylation shifts (Culvenor 1966; Booth *et al*., 1965).



60

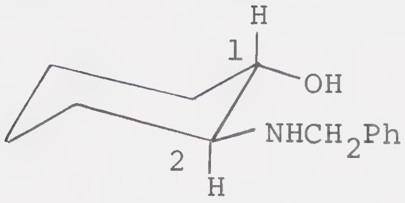
The use of the analogs (61), which show high conformational preferences, was also planned to aid these studies.



61

The compounds discussed below are described, in general, in the order of their synthetic availability.

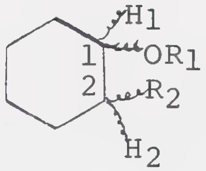
1. (±)-trans-2-Benzylaminocyclohexanol (38)



38a

The synthetic route used to prepare (38) (diaxial ring opening product of cyclohexene oxide with benzylamine) should result in a trans product of preferred conformation (38a). Only one methine signal could be resolved in the spectrum of the base in $CDCl_3$ (Table 1, No. 1) but its low field position and broad nature W_H = 12.5 Hz) indicated that it arose from the axial C-1 methine proton. The benzylic methylene signal of (38) was a quartet centered at 227 Hz (from TMS, recorded on Varian A-60D), typical of methylene in an asymmetric environment (Horobin et al., 1966), while a singlet was observed in the spectrum of the corresponding cis isomer (see subsection 10). The lower field methine signal was fairly well resolved and first order analysis showed that most of the coupling was due to two J = 9.5 Hz and one J = 4.5 Hz interactions typical of J_{aa} and J_{ae} (or J_{ee}) respectively.

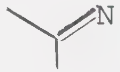
TABLE 1. PMR CHARACTERISTICS OF 2-AMINOCYCLOHEXANOL DERIVATIVES



No.	R_1	R_2	Isomer	PMR Signal[a] H_1[b] (W_H; Base Width)	PMR Signal[a] H_2[b] (W_H; Base Width)	Solvent
1	H	$NHCH_2Ph$	*trans*	191(12.5;30) ($J_{1,2}$ 9.5)	153-c	$CDCl_3$
2	H	NH_2	*trans*	191(20;40) ($J_{1,2}$ 9)	146(21;40) ($J_{1,2}$ 9)	D_2O
				185(13;35)	148(-;34)	$CDCl_3$
3	H	$NH_2 \cdot HCl$	*trans*	218(20;38) ($J_{1,2}$ 10)	179(21;39) ($J_{1,2}$ 10)	D_2O
4	H	NMe_2	*trans*	212(16;40) ($J_{1,2}$ 9.3)	151-d	D_2O
5	H	$NMe \cdot HCl$	*trans*	212(21;39)	200-d	D_2O
6	COMe	$NMe_2 \cdot HCl$	*trans*	310-e ($J_{1,2}$ 10)	208(24;40) ($J_{1,2}$ 11)	D_2O
7	COMe	$\overset{+}{N}Me\ I^-$	*trans*	311(16.5;41) ($J_{1,2}$ 8.5)	231(19;36) ($J_{1,2}$ 10)	D_2O

continued

TABLE 1. continued

No.	R_1	R_2	Isomer	PMR Signal[a] H_1[b] (W_H; Base Width)	 H_2[b] (W_H; Base Width)	Solvent
8		 Ph-NO_2-*p*	*cis*	287*(14.5;28)	253*(16;45)	DMSO-d_6
9	H	NHCO-Ph-NO_2-*p*	*cis*	f	f	DMSO-d_6
10	H	NHCO-Ph-NO_2-*p*	*trans*	f	f	DMSO-d_6
11	H	NH_2	*cis*	226(11;28)	166(13;29)	D_2O
12	H	NH_2·HCl	*cis*	247(7;18)	202(17;32)	D_2O
13	H	NMe_2	*cis*	260(8;14)	181-d	D_2O
14	H	NMe_2·HCl	*cis*	264(7;14)	204-d	D_2O
15	COMe	NMe_2·HCl	*cis*	324(8.5;13.5)	197(17;31)	D_2O
16	H	$NHCH_2Ph$	*cis*	236-g	155(13;24)	$CDCl_3$
17	COMe	$\overset{+}{N}Me_3$ I^-	*cis*	332(8.5;12.5)	212(16;30) ($J_{a,a}$ 16)	D_2O
18	H	$\overset{+}{N}Me_3$ I^-	*trans*	240(21;34) ($J_{1,2}$ 9.5)	216-d	D_2O
19	H	$\overset{+}{N}Me_3$ I^-	*cis*	285-e	213-d	D_2O

continued

TABLE 1. continued

No.	R_1	R_2	Isomer	PMR Signal[a] H_1[b] (W_H; Base Width)	H_2[b] (W_H; Base Width)	Solvent
20	$COCHPh_2$	NMe_2	*trans*	h	219(15;35)	$CDCl_3$
21	$COCHPh_2$	$NMe_2 \cdot HCl$	*trans*	297(18;33)	196(20;37)	$CDCl_3$
22	$COCHPh_2$	$\overset{+}{N}Me_3\ I^-$	*trans*	h	255(19;35)	$CDCl_3$
23	$COCHPh_2$	NMe_2	*cis*	319(7;15)	d	CCl_4
24	$COCHPh_2$	$NMe_2 \cdot HCl$	*cis*	332(65;16)	196(20;30)	$CDCl_3$
25	$COCHPh_2$	$\overset{+}{N}Me_3\ I^-$	*cis*	339(7;16)	266(14;36)	$CDCl_3$
26	$COC(OH)Ph_2$	NMe_2	*trans*	288(18;35)	188(12;35)	CCl_4
27	$COC(OH)Ph_2$	$NMe_2 \cdot HCl$	*trans*	302(17;35)	204(20;38)	DMSO-d_6
28	$COC(OH)Ph_2$	$\overset{+}{N}Me_3\ I^-$	*trans*	307(17;35)	219(18;35)	DMSO-d_6
29	$COC(OH)Ph_2$	NMe_2	*cis*	323(6;15)	d	CCl_4
30	$COC(OH)Ph_2$	$NMe_2 \cdot HCl$	*cis*	327(7;15)	202(10;36)	DMSO-d_6
31	$COC(OH)Ph_2$	$\overset{+}{N}Me_3\ I^-$	*cis*	332(7;17)	219 (17;31)	DMSO-d_6

[a] All data were recorded on a Varian A-60D instrument at normal temperature.

continued

TABLE 1. continued

[b] Center of multiplets is given in Hz from TMS. Hz is also used for J values, width at half height (W_H) and base width. J values were obtained by first order analysis when possible and hence are not necessarily the accurate values.

[c] Overlapping with ring proton signals.

[d] Overlapping with N-methyl signals.

[e] Obscured by water peak.

[f] Two methine signals overlap each other.

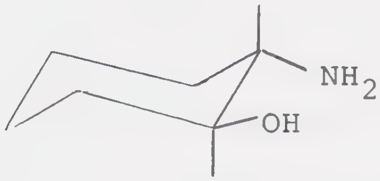
[g] Obscured by the CH_2 signal of $\underline{CH_2}Ph$.

[h] Obscured by the CH signal of $\underline{CH}Ph_2$.

[*] The C-1 and C-2 positions of the cyclohexane derivatives correspond to the C-5 and C-4 positions of the oxazoline respectively.

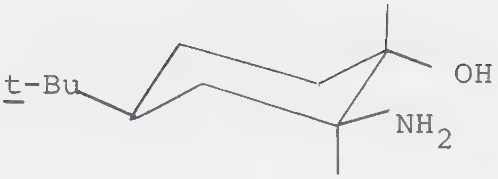
2. (±)-trans-2-Aminocyclohexanol (35)

The spectrum of this compound in D_2O and in $CDCl_3$ derived from (38) by catalytic debenzylation, was consistent with the trans diequatorial conformation (35a)



35a

(Table 1, No. 2). Both methine signals were downfield of the main ring proton band and well resolved. Their dimensions and first order analysis established their axial conformation. Its PMR spectrum in $CDCl_3$ displayed a well resolved C-1 methine signal centered at 185 Hz (W_H = 13 Hz, base width = 35 Hz) and a broad C-2 methine signal at 148 Hz (base width 34 Hz), the latter being obscured by the presence of a hydroxyl proton resonance. The shape and the location of the two methine signals were almost exactly reproduced in the spectrum of trans-2-amino-trans-4-t-butylcyclohexanol (74d) (synthesis of this compound see section iii of Chapter III); in this compound the C-1 proton resonance was centered at 182 Hz (W_H = 20 Hz, base width = 35 Hz) and the C-2 proton resonance, also obscured by the hydroxyl proton peak,



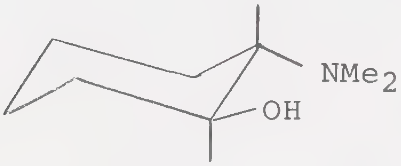
74d

centered at 147 Hz (base width = 35 Hz). These data further show that conformer (35a) is preferred.

Hydrochloride

The methine signals in the hydrochloride of (35) had a very similar appearance to those of the free base except both were shifted downfield (Table 1, No. 3).

3. (±)-trans-2-Dimethylaminocyclohexanol (28)

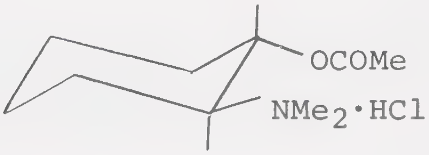


28a

In the spectra of this compound (solvents D_2O or CCl_4) the higher field methine proton was obscured by the NMe_2 signal (a sharp singlet). The lower field C-1

methine resonance was well resolved, however, and had dimensions typical of an axial proton (Table 1, No. 4), a result supporting 28a as the preferred conformation. This signal had a similar shape in the spectrum of the hydrochloride salt in D_2O. In the same spectrum, the NMe_2 signal formed two sharp singlets of equal intensity separated by 7 Hz (Table 2, No. 1). This duplication was not due to $H\overset{+}{N}Me$ coupling because the spectrum was recorded in D_2O (fast proton exchange) and showed the two N-methyl groups to be non-equivalent. This point is discussed further when the spectra of related cis hydrochlorides are considered.

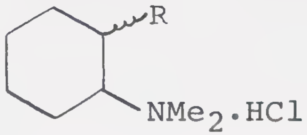
4. (±)-trans-2-Dimethylaminocyclohexyl Acetate Hydrochloride (62)



62

In this case (Table 1, No. 6) the spectrum showed the usual methine multiplets. The C-1 resonance was 74 Hz downfield of the corresponding signal in the alcohol hydrochloride, the magnitude of the shift being typical

TABLE 2. N-METHYL SIGNALS IN THE PMR SPECTRA OF HYDROCHLORIDES OF DIMETHYLAMINOCYCLOHEXANE DERIVATIVES



No.	R	Isomer	PMR Signals of NMe_2[a]	Separation of NMe Signals[b]	Solvent
1	OH	*trans*	173.5, 166.5[c]	7	D_2O
2	OCOMe	*trans*	173.5, 165[c]	8.5	D_2O
3	OH	*cis*	175.5, 173[c]	2.5	D_2O
4	OCOMe	*cis*	174, 171[c]	3	D_2O
5	$OCOCHPh_2$	*trans*	155, 146[c]	9	$CDCl_3$
6	$OCOCHPh_2$	*cis*	159, 144[c]	15	$CDCl_3$
			154	-	D_2O
7	$OCOC(OH)Ph_2$	*trans*	154[d]		DMSO-d_6
8	$OCOC(OH)Ph_2$	*cis*	161[d]		DMSO-d_6
9	H		170		D_2O
			166		$CDCl_3$

[a] All data were recorded on a Varian A-60D instrument at normal temperature. Chemical shift is given in Hz from TMS.

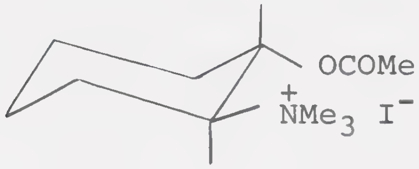
[b] Separation of the non-equivalent NMe resonance signals was measured in Hz.

[c] Doublet of doublets (J ∿5Hz) or two singlets indicative of non-equivalence of the NMe_2 group.

[d] Overlap of NMe_2 signals with the solvent signal.

of the acylation of a secondary alcohol (Culvenor, 1966). In contrast, the C-2 shift (ca. 24 Hz) was much less. Again, the NMe groups were magnetically non-equivalent, and their signals were separated by 8.5 Hz (Table 2, No. 2). The NMe_2 doublet collapsed to one singlet when ammonia was added.

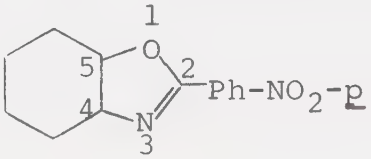
5. (±)-trans-2-Dimethylaminocyclohexyl Acetate Methiodide (30)



30a

The C-1 and C-2 methine signals of the spectrum of this methiodide in D_2O were both well resolved and typical of axial protons (Table 1, No. 7). The NMe_3 resonance was a sharp singlet. Again (30a) is a preferred conformation.

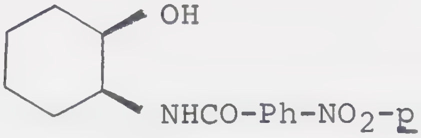
6. (±)-2-p-Nitrophenyl-4,5-cis-cyclohexanoöxazoline-2 (37)



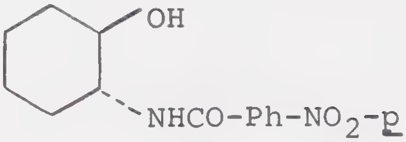
37

Chemical evidence for the geometry of the *cis* oxazoline (37) obtained from (±)-*trans*-2-*p*-nitrobenamidocyclohexanol (36) has been described in the previous text. The PMR spectrum of the oxazoline (37) (Table 1, No. 8) showed two 1-proton multiplets in DMSO-d_6. On the basis of Weinberger and Greenhalghs' (1963) assignment that the chemical shift of 5-methylene group in monocyclic oxazolines is lower than that of 4-methylene, the multiplet at lower field (center at 287 Hz) was assigned to the C-5 proton and that at higher field (center at 253 Hz) to the C-4 proton. Both signals were broad and the lower field signal was a well resolved sextet (J = 8.5, 5 and 5 Hz). Interpretation of coupling constant data in terms of conformation is difficult because oxazoline formation distorts the cyclohexane ring. Long range coupling between the C-4 proton and aromatic protons may be responsible, in part, for the broad nature of the resonance signal of the C-4 proton, since long range coupling across a conjugated system is a well-known fact; the operation of long range coupling between the protons at C-4 and methyl protons attached to C-2 has already been proposed for related oxazolines (Weinberger and Greenhalgh, 1963).

7. (±)-*cis*-2-*p*-Nitrobenzamidocyclohexanol (41) and its *trans* isomer (36)



41



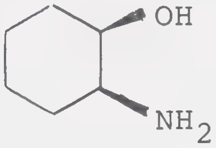
36

The *cis* amide (41) (Table 1, No. 9) (derived from the oxazoline 37) had a PMR spectrum in DMSO-d_6 which showed coincident methine signals; N-acylation causes the C-2 methine proton to move downfield (Booth *et al.*, 1965). In the *trans* isomer (Table 1, No. 10) the two methine signals also overlapped but less extensively and the overall signal width was greater than that seen for the *cis* methine protons, in accord with their configurational difference.

Booth *et al.* (1965) reported that the sharpness of the ring proton signals in *cis*-2-alkylcyclohexylamines is quite marked and can be used to distinguish such molecules from their *trans* isomers; in these isomers ring proton signals are generally broad. A sharp ring proton signal was shown in the PMR spectrum of the *cis* isomer (41), while the ring protons of the *trans* compound (36) had a very broad resonance. The configuration of (41) as a *cis* isomer is, therefore, further confirmed. As regards

the cis oxazoline (37), its ring proton resonance was moderately sharp, not so sharp as that of the cis isomer (41), when compared with that of the trans isomer (36).

8. (±)-cis-2-Aminocyclohexanol (34)



34

The spectrum of the cis aminoalcohol (34) (Table 1, No. 11) obtained from the cis amide (41) in D_2O showed two well separated 1-proton bands centered near 226 and 166 Hz respectively and assigned to the C-1 and C-2 methine protons. These were both lower field than the corresponding signals of the trans isomer (35) (Table 1, No. 2) and their narrower, but similar, dimensions indicates that similar populations of the two forms (34a) and (34b) exist in D_2O solution (see Figure 2a). The axial OH component (34a) narrows the C-1 methine proton signal relative to its width in the trans isomer, the C-2 signal being narrowed as a result of the axial-NH_2 population. In the spectrum of the hydrochloride (63)

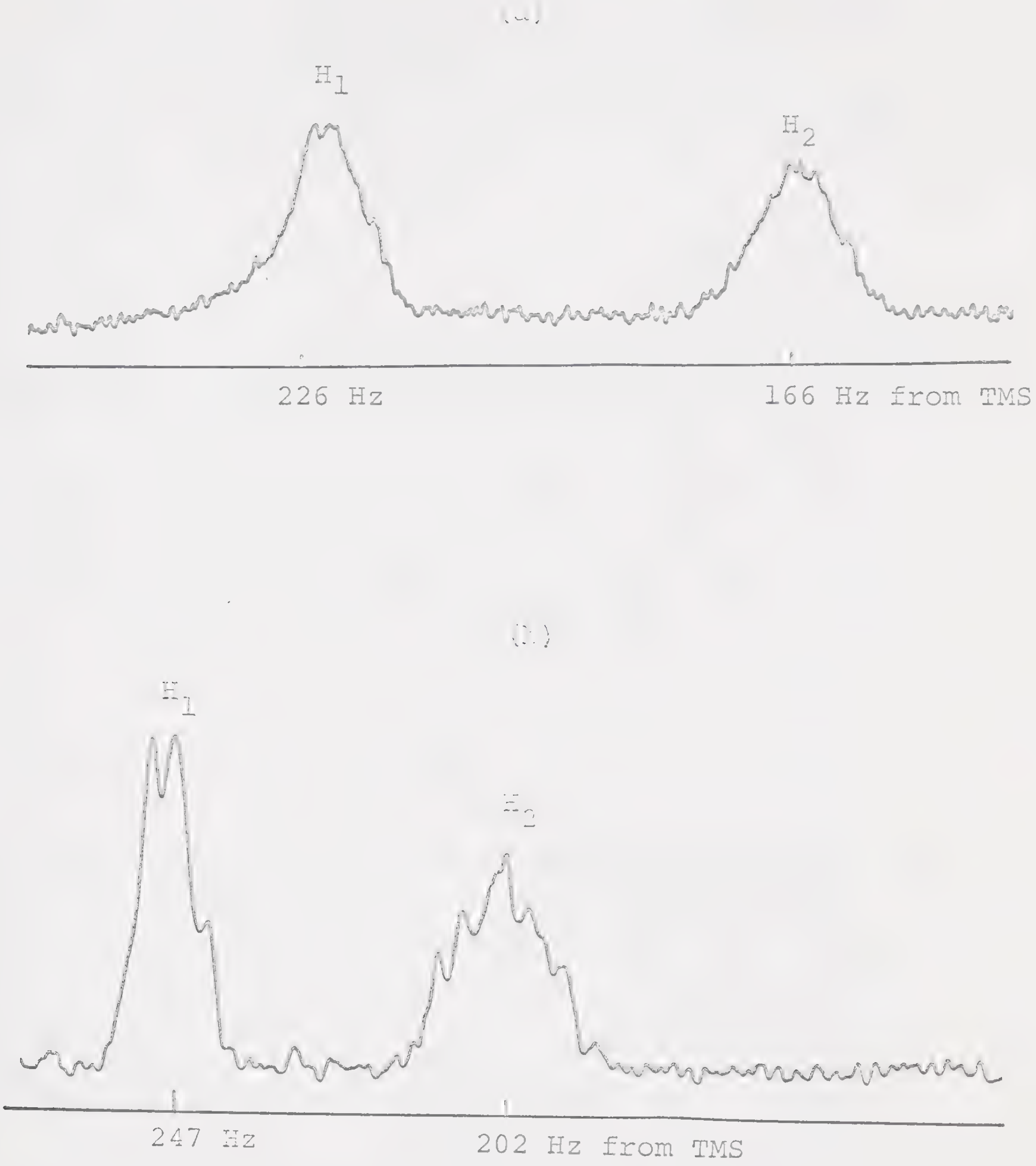
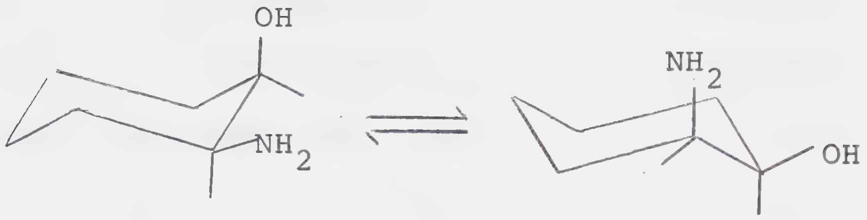
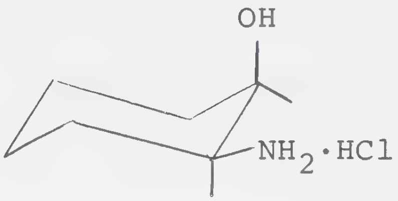


FIGURE 2. C-1 and C-2 methine proton signals in the PMR spectra of (±)-*cis*-2-aminocyclohexanol (a) and its hydrochloride (b) in D_2O. Recorded on Varian A-60D.



34a 34b

(Table 1, No. 12), the C-1 multiplet was distinctly the narrower of the two (Figure 2b) and this result shows that



63

the equatorial amino conformer (63a) preponderates when its size is increased by protonation (and consequent increased solvation). In the salt both methine signals moved downfield as a result of the more electronegative influence of protonated, compared with free, nitrogen.

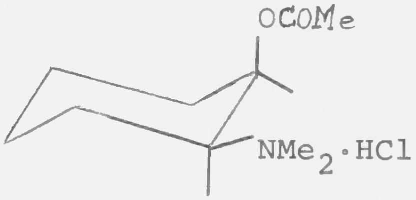
9. (±)-*cis*-2-Dimethylaminocyclohexanol (29)

In the spectrum of the tertiary aminoalcohol (29) (Table 1, No. 13) in D_2O, only the C-1 methine proton could be resolved. Its dimensions indicate a preferred

equatorial NMe_2 conformation. The NMe_2 signal in the spectrum of the hydrochloride of (29), was composed of two singlets, as in the spectrum of the corresponding trans hydrochloride but the separation was much less (Δ2.5 Hz for cis, 7 Hz for trans) (Table 2, No. 3).

10. (±)-cis-2-Dimethylaminocyclohexyl Acetate Hydrochloride (64)

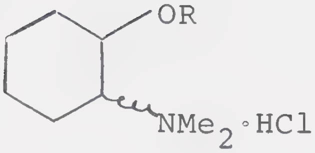
The spectrum of this salt in D_2O showed a narrow C-1 band (low field because of the acylation shift) and a broad C-2 band, in support of the preferred conformation (64a) (Table 1, No. 15). The NMe_2 signal (two



64a

singlets of separation 3 Hz) (Table 2, No. 4) was about the same as that of the corresponding amino alcohol salt; in the hydrochloride of the trans ester (62) the NMe singlet separation was 8.5 Hz.

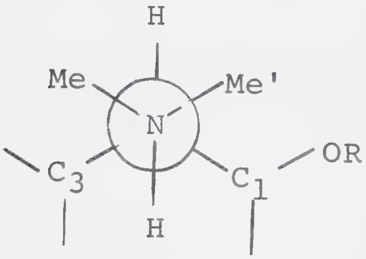
The two NMe groups differ in their environments in both isomeric hydrochlorides (65), but the extent of non-equivalence is greater in the trans isomers. This



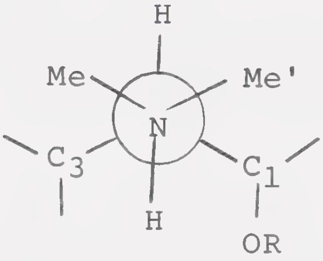
R = H, Ac

65

fact provides an additional means of configurational differentiation. Probable conformations for *trans* (65a) and *cis* (65b) salts are shown below. In the



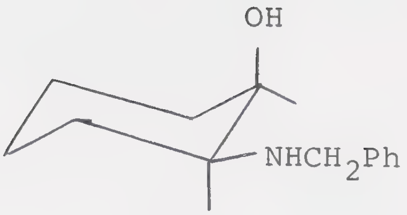
65a



65b

trans conformer, magnetic non-equivalence of the NMe groups must be due chiefly to the RO group which is much closer to Me' than to Me. In the *cis* conformer, Me' is further removed from OR and hence the environmental difference between Me and Me' should be less in this isomer.

In the spectrum of (±)-*cis*-2-benzylaminocyclohexanol (66) (Table 1, No. 16), the benzylic methylene

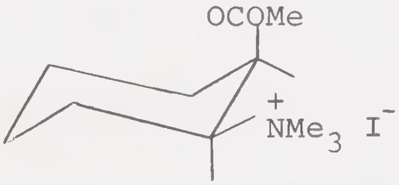


66

signal was a singlet, in contrast to the quartet seen in the spectrum of the corresponding trans compound (38). This may also be attributed to its relatively symmetrically magnetic environment in the former and asymmetry in the latter, as discussed above.

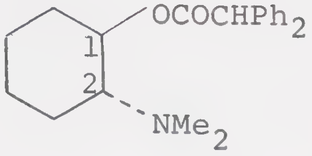
11. (±)-cis-2-Dimethylaminocyclohexyl Acetate Methiodide (31)

The spectrum of the cis isomer (31) (Table 1, No. 17) in D_2O showed a narrow C-1 methine band and a broad C-2 band which clearly establishes (31a) as the preferred conformation of the salt in D_2O.



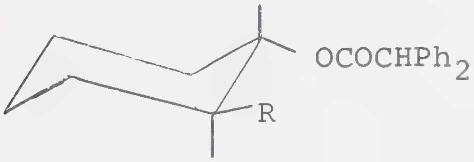
31a

12. (±)-trans-2-Dimethylaminocyclohexyl Diphenylacetate (67) and Its Derivatives



67

Both C-1 and C-2 protons of the free base (67), its hydrochloride (47) and methiodide (49) (Table 1, No. 20, 21 and 22) had a broad and resolvable signal, indicating that the preferred conformations of these compounds are those (68) in which the two methine protons are in the axial position.

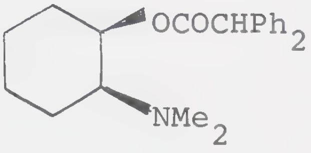


$R = NMe_2,\ NMe_2 \cdot HCl,\ \overset{+}{N}Me_3\ I^-$

68

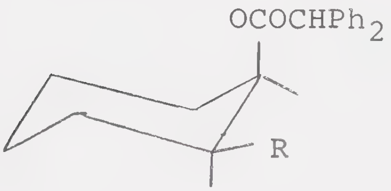
Non-equivalence of the NMe_2 resonance signal was not observed in the free base but was clearly apparent in the spectrum of the hydrochloride (Table 2, No. 5).

13. (±)-cis-2-Dimethylaminocyclohexyl Diphenylacetate (69) and Its Derivatives



69

In the spectra of the free base (69), its hydrochloride (48) and methiodide (50) (Table 1, No. 23, 24 and 25), a narrow one-proton signal near 330 Hz and a higher field one-proton broad signal near 200 Hz were present. This shows that the conformer (70) is the preferred conformation of these compounds.



R = NMe_2, $NMe_2 \cdot HCl$, $\overset{+}{N}Me_3\ I^-$

70

Non-equivalence of the NMe_2 resonance was shown in the hydrochloride salt (Table 2, No. 6), as anticipated from the previous discussion (the two non-equivalent NMe doublets collapsed to one sharp singlet when the

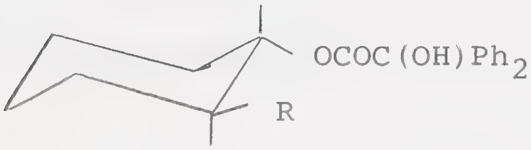
solvent was changed from $CDCl_3$ to D_2O). Separation of the NMe doublets (Δ=15 Hz) of this hydrochloride was greater than that of the corresponding trans isomer (47) (Δ=9 Hz). The order of difference is thus the reverse of that seen in hydrochlorides of the cis and trans alcohol and acetate analogs (Table 2, No. 1, 2, 3 and 4). The small downfield shift of the NMe signals in the alcohol and acetate analogs as compared with that of dimethylaminocyclohexane hydrochloride (Table 2, No. 9) suggests that the hydroxy and acyloxy oxygen atoms have a small deshielding influence upon the NMe protons of these compounds. Both NMe groups will suffer this influence but the deshielding difference between the two will be greater in the trans case as already discussed.

In the diphenylacetates (47 and 48), however, the aromatic groups have a more significant shielding effect than the acyloxy oxygen atom; this must be a screening effect since the NMe signals of the aromatic esters are markedly upfield (about 20 Hz in $CDCl_3$) of NMe in dimethylaminocyclohexane hydrochloride. This argument can be used to explain the observed reversed non-equivalent NMe separation in the diphenylacetate series. In the trans isomer (47) models reveal that the aromatic rings of the acyl moiety may be directly beneath both NMe groups without generating serious non-bonded interactions with the cyclohexane ring protons and it is probable that each

will receive similar shielding contributions. In the *cis* isomer (48), however, the axial orientation of the ester group will result in the bulky aromatic feature being deflected away from the cyclohexane ring; in consequence, the farther removed NMe group (cf Me in 65b) will be less subject to aromatic screening than the closer group (cf Me′ in 65b), leading to a more pronounced chemical shift difference between the NMe groups in the *cis* isomer.

14. (±)-*trans*-2-Dimethylaminocyclohexyl Benzilate (51) and Its Derivatives

Again, based upon the PMR data, the preferred conformation (71) was assigned to the free base (51), its



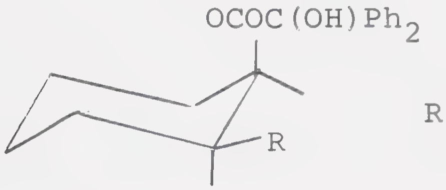
R = NMe_2, $NMe_2 \cdot HCl$, $\overset{+}{N}Me_3\ I^-$

71

hydrochloride (55) and its methiodide (57) (Table 1, No. 26, 27, and 28). In the spectrum of the hydrochloride in DMSO-d_6 the NMe_2 signal could not be clearly resolved because it overlapped the solvent signal (Table 2, No. 7).

15. (±)-*cis*-2-Dimethylaminocyclohexyl Benzilate (52) and Its Derivatives

The resonance signals of the C-1 and C-2 protons, a narrow signal at lower field and a broad signal at higher field, were the same as those seen in the *cis* diphenylacetate series and the conformation (72) of this series (52, 56, 58) (Table 1, No. 29, 30, 31) is thus favored. The NMe_2 signal in the spectrum of the hydrochloride (56) was a broad singlet but was obscured by the solvent signal (Table 2, No. 8).

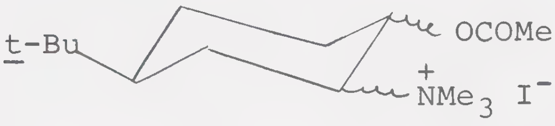


$R = NMe_2,\ NMe_2 \cdot HCl,\ \overset{+}{N}Me_3\ I^-$

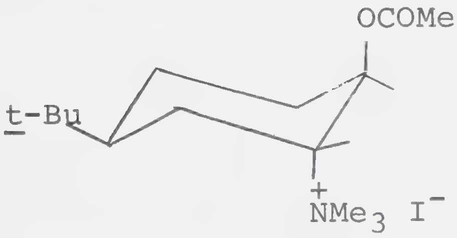
72

iii) SYNTHESIS OF 4-*t*-BUTYL-2-AMINOCYCLOHEXANOLS AND THEIR DERIVATIVES

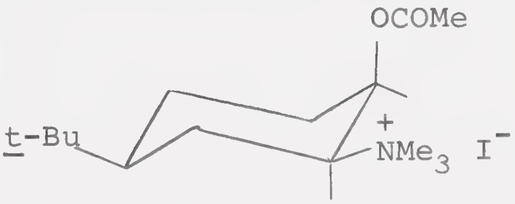
4-*t*-Butyl-2-dimethylaminocyclohexyl acetate methiodide (73) has four stereoisomers (73a, 73b, 73c, and 73d) as shown below (chair forms are drawn on the assumption that their conformations have not been deformed):



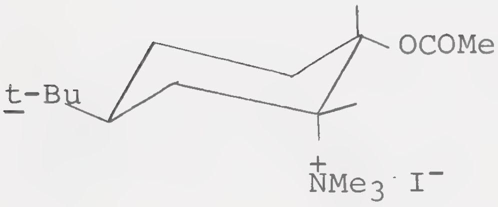
73



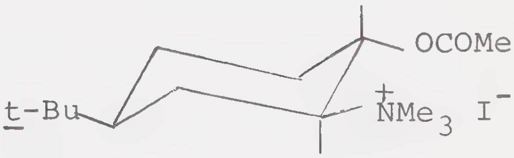
73a



73b

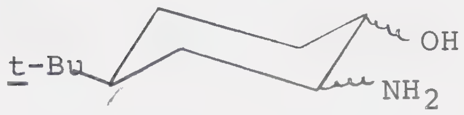


73c

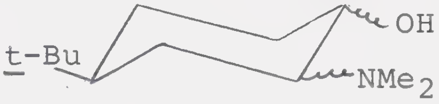


73d

The reaction pathway for preparing these stereoisomers (73a, 73b, 73c and 74c) may be via the free aminoalcohols (74) or the dimethylaminoalcohols (75) which can be obtained from stereospecific reactions.

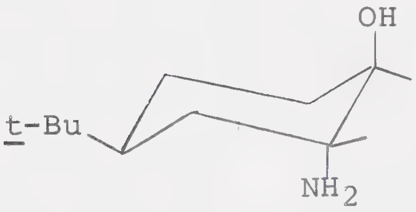


74

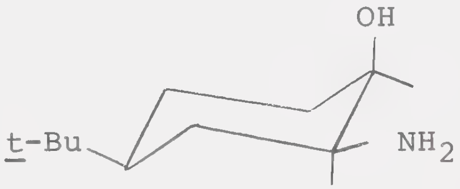


75

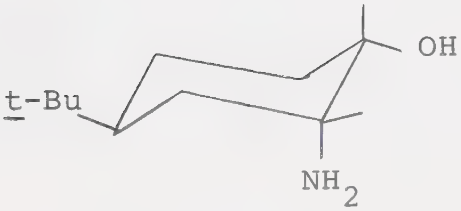
Sicher *et al.* (1961) have given the detailed procedure for the synthesis of the free aminoalcohols (74a, 74b, 74c and 74d). A brief review of the Czech workers'



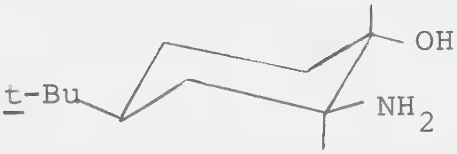
74a



74b



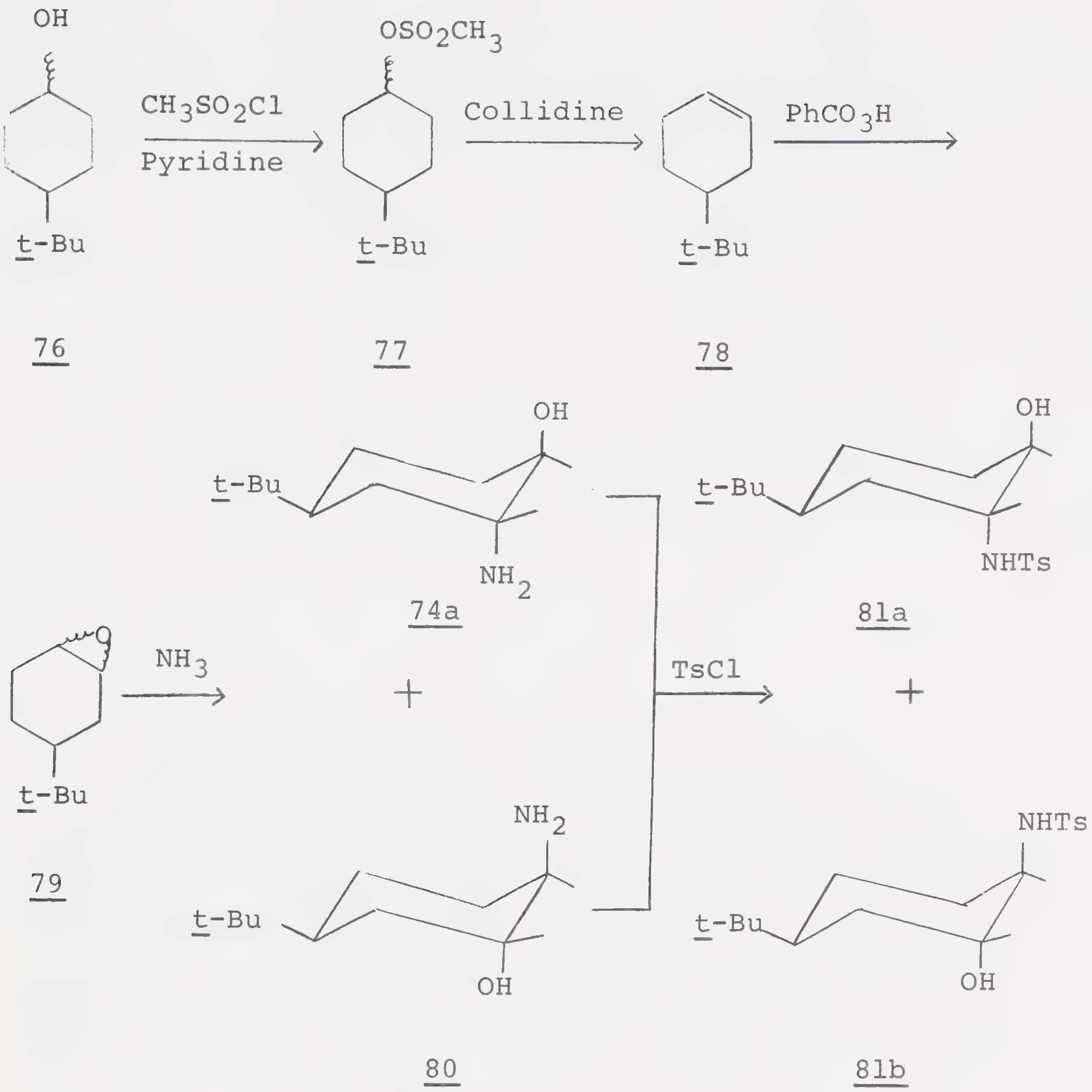
74c



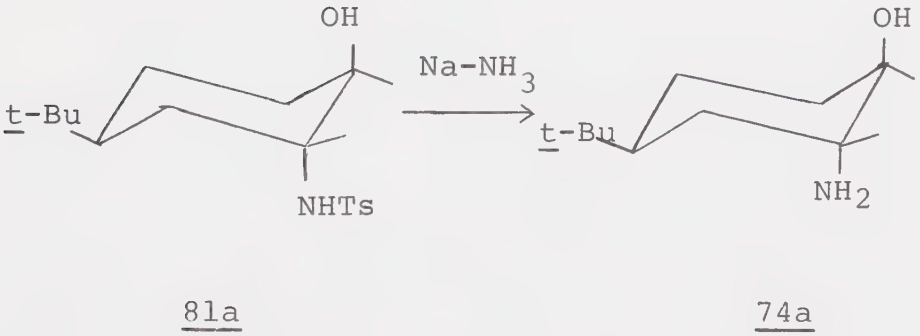
74d

synthesis of these isomers is given in the following text.

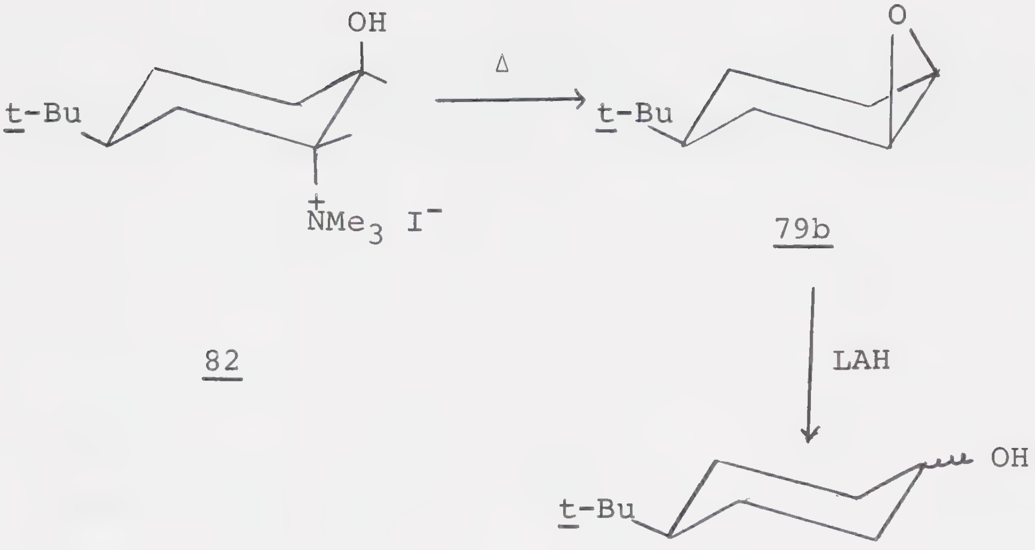
trans-2-Amino-*cis*-4-butylcyclohexanol ("O^a, N^a", **74a**) was prepared as follows: treatment of a mixture of *cis* and *trans*-4-*t*-butylcyclohexanol (**76**) with methanesulfonyl chloride; reflux of the resultant methanesulfonate (**77**) in collidine to give 4-*t*-butylcyclohexene (**78**); epoxidation of the cyclohexene; ammonolysis of a mixture of the *trans* and *cis* 4-*t*-butylcyclohexene oxide (**79**) thus formed to produce a mixture of (**74a**) and its positional isomer (**80**); and separation of the positional isomers by way of N-tosyl derivatives (**81a** and **81b**) and detosylation of (**81a**) yielding pure (**74a**). The configuration of (**74a**) was assigned on the basis of the rule of diaxial opening of epoxides (Barton and Cookson, 1956; Parker and Isaacs, 1959). Confirmation of the positional isomer as (**74a**) was made by pyrolysis of the corresponding quaternary trimethylammonium base (**82**) to give the *cis* epoxide (**79b**) (Sicher and Pánková, 1955; Svoboda and Sicher, 1958) and by reducing the epoxide thus formed with lithium aluminum hydride to the 4-hydroxy isomer (**76**) (*cis* is the major product), a process known to proceed stereospecifically by axial attack (Fürst and Plattner, 1949; Rickborn and Quartucci, 1964).



76 77 78 79 74a 80 81a 81b



81a 74a



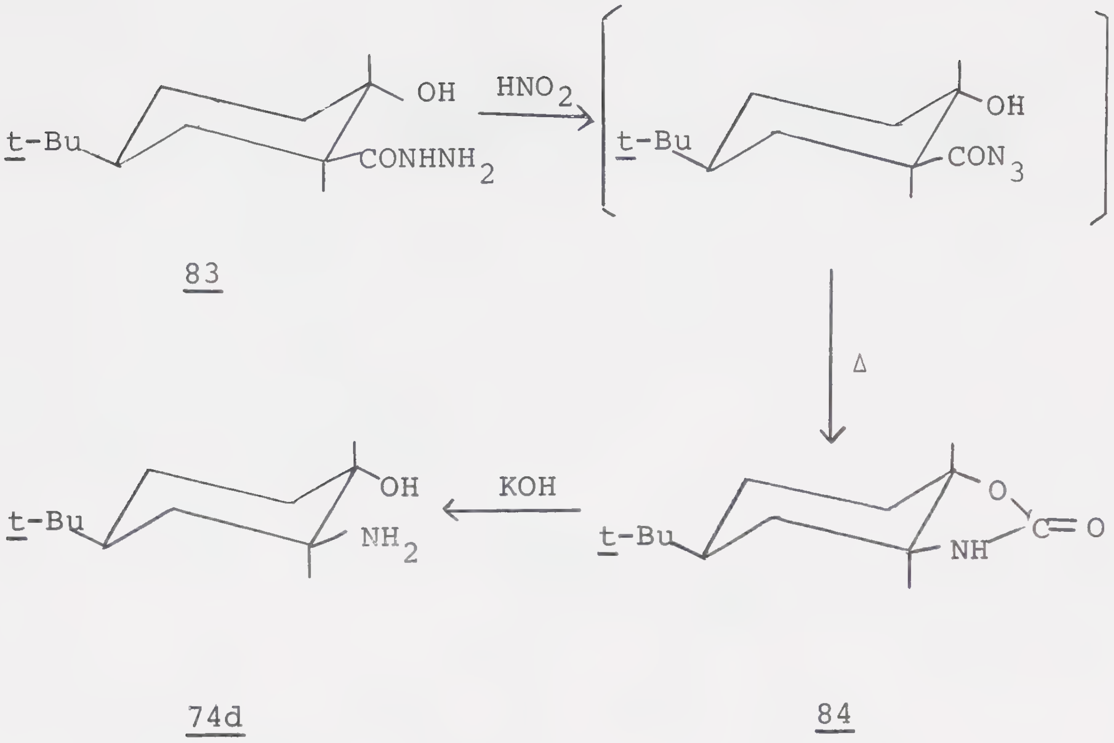
82

79b

76

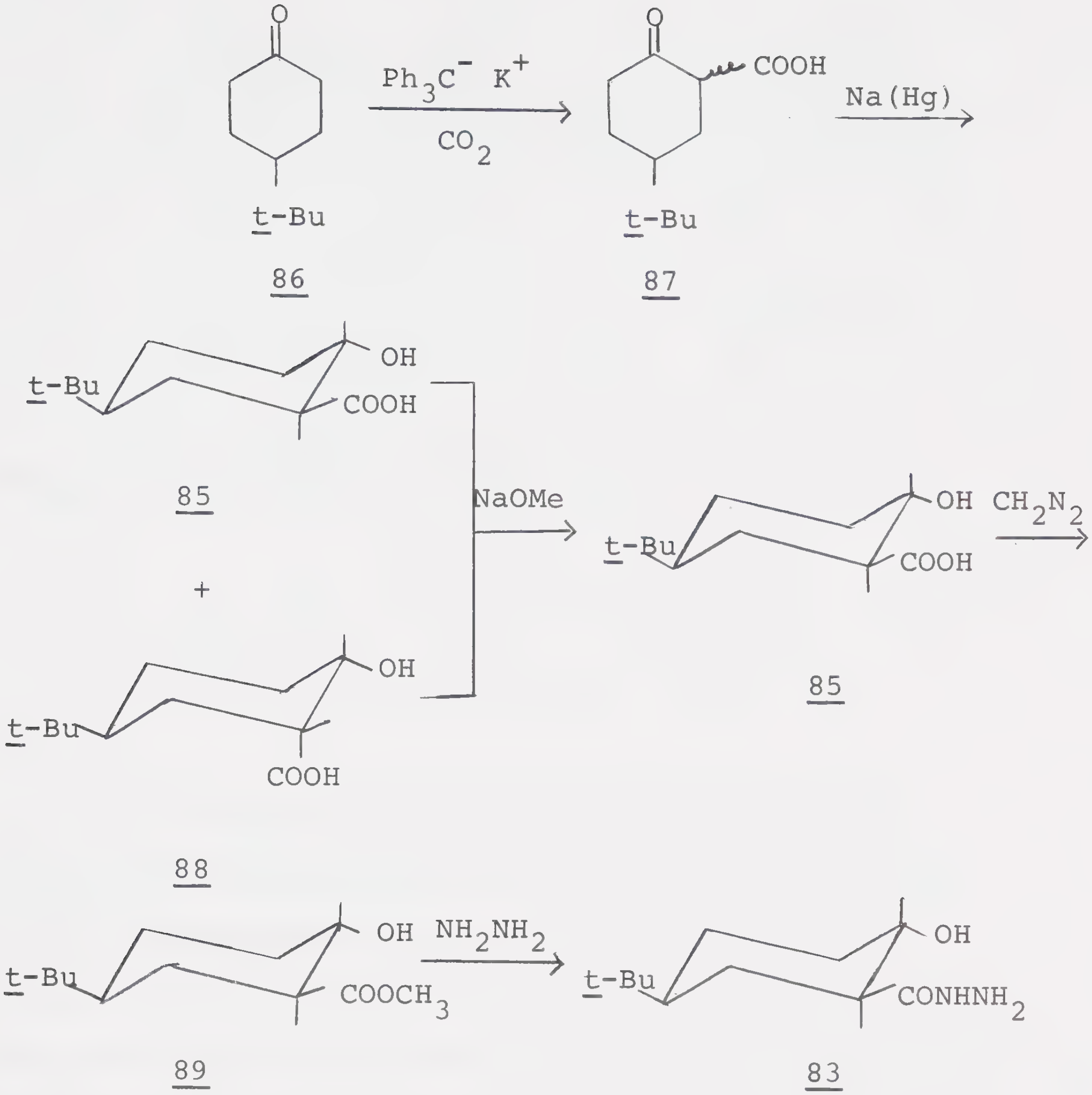
trans-2-Amino-trans-4-t-butylcyclohexanol ("O^e, N^e", 74d) was obtained by Curtius degradation of the corresponding isomer of cis-t-butyl-trans-2-hydroxycyclohexanecarboxylic acid hydrazide (83): treatment of the hydrazide with nitrous acid, decomposition of the azide formed to give the cyclic urethane (84), and the basic hydrolysis of the urethane.

cis-5-t-Butyl-trans-2-hydroxycyclohexanecarboxylic acid (85) was derived from reduction of 5-t-butylcyclohexan-2-onecarboxylic acid (87) with sodium amalgam and equilibration of the thus formed hydroxyacid mixture (85 and 88) with sodium methoxide. The acid (85) was esterified with diazomethane, and the esterified product (89)

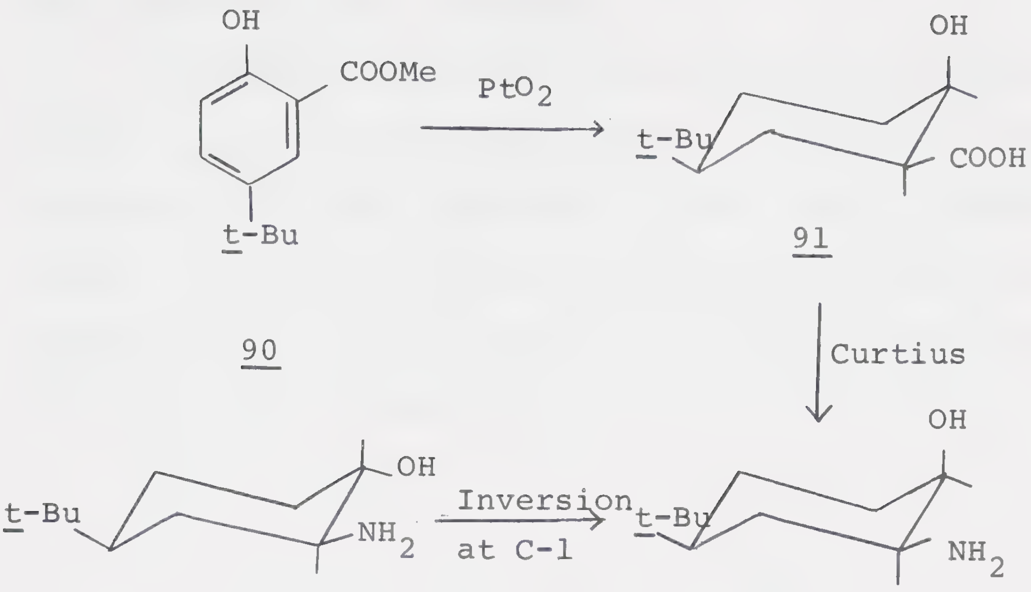


was then converted to the hydrazide (83). 5-*t*-Butylcyclohexan-2-onecarboxylic acid (87) was prepared by carboxylation of 4-*t*-butylcyclohexanone (86), triphenylmethyl potassium being used as the condensing agent. The assignment of configuration to these acids will be discussed later.

trans-5-*t*-Butyl-2-*cis*-hydroxycyclohexanecarboxylic acid (88) isolated in the previous route was converted by Curtius procedure, into the corresponding aminoalcohol (74c), *cis*-2-amino-*trans*-4-*t*-butylcyclohexanol ("O^e,N^a"), which was also identical with that which resulted from (74a) ("O^a,N^a") via the oxazoline inversion procedure (described in the simple cyclohexane series).



cis-2-Amino-cis-4-t-butylcyclohexanol ("O^a,N^e" 74b) was obtained from (74d) by the oxazoline inversion procedure and also by Curtius degradation of the corresponding hydroxy-acid (91) which was made by hydrogenation of methyl p-t-butylsalicylate (90) on platinum oxide (scheme for this synthesis shown below).



90

91

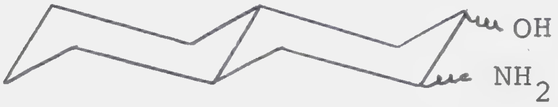
74d

74b

The assignment of configuration to the three hydroxy-acids (85, 88 and 91) were made on the basis of the relative stabilities of their esters towards epimerization and measurement of the rate of chromic acid oxidation of the acids. The esters of (85) and (91) which did not isomerize when refluxed with sodium methoxide were assigned an equatorial carboxyl group, while the ester of (88) which did isomerize has the carboxyl group in the axial position, since the equatorial substitution is generally more stable than the axial one (Eliel *et al.*, 1965). The rates of chromic acid oxidation will provide information regarding the configuration of the hydroxyl group, an equatorial hydroxyl group being known to be oxidized slower than an axial

one (Schreiber and Eschenmoser, 1955).

In the present work, stereospecific syntheses of the 2-amino-4-t-butylcyclohexanol isomers and their derivatives followed some parts of work done by Sicher et al. (1961) with modifications and also traced some routes used in the synthesis of the isomeric 3-amino-2-decalols (92) (Smissman et al., 1966).



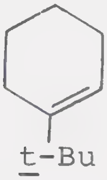
92

trans-2-Amino-cis-4-t-butylcyclohexanol ("O^a,N^a", 74a) and Its Derivatives

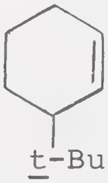
The route designed by Sicher et al. (1961) for making (74a) was modified in respect of the epoxidation of 4-t-butylcyclohexene (78) and the ammonolysis of 4-t-butylcyclohexene oxide (79). The 4-t-butylcyclohexanol (76) used in this work was a commercial sample from Aldrich composed of 67% of the trans isomer and 28% of the cis isomer.

In view of the greater simplicity of acid-catalyzed elimination of secondary alcohols compared with Sicher's

two-step procedure, 4-t-butylcyclohexanol (76) was heated with 85% orthophosphoric acid and the reaction driven to completion by distilling the water formed during the dehydration process. The PMR spectrum of the resultant olefin (93) in CCl_4 showed two vinylic signals, 336 Hz (broad doublet) and 324 Hz (broad signal), and two t-butyl singlets, 52 Hz and 61 Hz, the intensities of which varied from batch to batch. The higher field t-butyl and lower field vinylic signals were coincident with those of the 4-t-butylcyclohexene (78) obtained from the corresponding methanesulfonic acid ester (77). Since isomerization of olefins is probable under acid conditions, the olefin (93) thus formed may consist of a mixture of 2-, 3-, and 4-t-butylcyclohexenes (93a, 93b and 78) and the latter two might be responsible for the t-Bu singlet at 52 Hz.



93a



93b

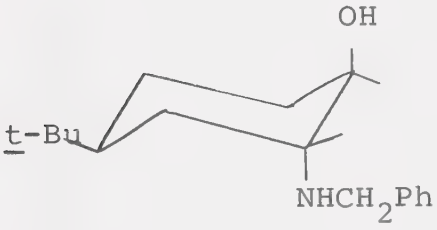
The probability of isomerization was confirmed by PMR studies of the products isolated after different periods of heating. The longer the heating, the more intense the singlet at 61 Hz relative to that of 52 Hz (the

change in intensities of the two vinylic signals was not so pronounced as that of the t-butyl resonance). The reason that only two t-butyl singlets were present for three isomers is probably because of little difference in the magnetic environments of t-butyl groups in the 3- and 4-ene isomers (93b and 78). The alkenes (93) derived from the alcohol (76) after acid treatment gave an epoxide product (94) which contained at least three isomers as seen by the three separate t-butyl signals in its PMR spectrum in CCl_4 (50, 53, and 58 Hz, that at highest field being major; no vinylic signals). The relative intensities of these three signals were also variable from batch to batch. The pure positional isomer mixture of cis and trans 4-t-butylcyclohexene oxide (79), prepared by following Sicher's method, displayed only one t-butyl signal at 50 Hz (CCl_4). The lower field t-butyl signals in the epoxide mixture obtained from the t-butylcyclohexene isomeric mixture are probably due to the presence of positional isomers of the epoxide (79).

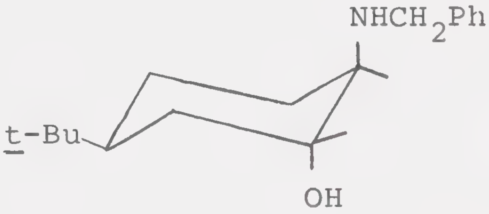
The preparation of perbenzoic acid by peroxidation of benzoic acid with 50% hydrogen peroxide in the presence of methanesulfonic acid gave a low yield (35%) not anticipated from the literature (85-95% yield) (Silbert *et al.*, 1963). Rickborn and Quartucci (1964) made the epoxide (79) by using commercial m-chloroperbenzoic acid. m-Chloroperbenzoic acid was not commercially

available at the time of these experiments, so this pathway could not be investigated. During the preparation of this epoxide (79), a report that epoxides could be synthesized by reacting olefins with 40% peracetic acid (commercially available) in the presence of anhydrous sodium carbonate (Crandall and Lin, 1968) was noticed. This method was employed to make the epoxides (79 and 94) and it was found that the yield was very good (above 80%).

Similar to the preparation of (±)-trans-2-aminocyclohexanol (35), the aminoalcohols (74a and 80) were obtained by catalytic debenzylation of the corresponding benzylaminoalcohols (95a and 95b), the hydrochlorides (96a and 96b) being used to separate positional isomers (discussed in the next paragraph). Sicher's method (1961), namely N-tosylation and N-detosylation of the primary aminoalcohols, also gave the pure isomer (74a).



95a

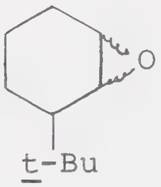


95b

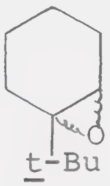
Ring opening of the pure positional epoxide (79) with benzylamine, assumed to proceed according to the known diaxial rule (Barton and Cookson, 1956; Parker and Isaacs, 1959), gave the corresponding benzylaminoalcohols (95a and 95b) in 70% yield. The PMR spectrum of the crude mixture of the benzylaminoalcohol hydrochlorides (96a and 96b) in $CDCl_3$ displayed two *t*-butyl singlets (50 Hz and 52.5 Hz) of similar intensities, the two singlets coinciding in water. Fractional crystallization of the two isomer salts (96a and 96b) gave one of the isomers in a pure condition. The isomer (96a) which separated first formed hexagonal shaped crystals which were large enough to allow their physical separation from the other isomer (96b) (this crystallized in prisms) when the former was contaminated with the latter (structural proof is given later). The *t*-butyl resonance signal of (96a) appeared at 50 Hz. In the PMR spectra of the total mixture of the free aminoalcohols (74a and 80), derived from the debenzylation of a mixture of (95a) and (95b), in $CDCl_3$ or in DMSO-d_6, only one singlet for the *t*-butyl groups was seen. This coincidence of *t*-butyl singlet was also seen in the spectra of the mixture of the benzylaminoalcohols, (95a) and (95b), run in $CDCl_3$, CCl_4 or DMSO-d_6. The *t*-butyl signals in the spectrum of the N-tosylated primary aminoalcohol mixture (74a and 80) were well separated and could also be used for differentiation purposes (that at 43 Hz was attributed to 81a

and that at 48 Hz to 81b, in solution of DMSO-d_6).

Reaction of the epoxide mixture (94) derived from the isomerized olefin mixture (93) with benzylamine afforded a 60% yield of the ring-opened product, derivatives of which (hydrochlorides and N-tosylates of the debenzylated product) had the same PMR spectra as those prepared from the pure 4-t-butylcyclohexene (78). When the reaction mixture was subject to distillation, the first fraction (b.p. 81-86°/16 mm) was identified as a mixture of the starting materials from its PMR spectrum in $CDCl_3$ in which two strong separate t-butyl singlets (55 and 57 Hz) appeared. In this spectrum, t-butyl signals at 55 and 57 Hz remained while the signal at 50 Hz, due to the epoxide (79) was absent; this result indicates that the epoxide isomers (94a and 94b) undergo the ring opening reaction less readily.



94a

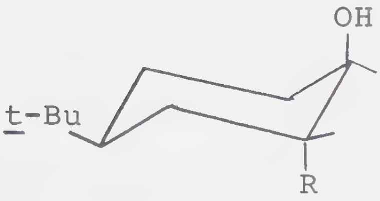


94b

The second fraction (b.p. 140-149°/0.1 mm) was composed of the required epoxide (79) ring opened product.

Assignment of structure to (74a) synthesized by

Sicher's procedure was achieved by comparing the melting points of derivatives of the debenzylated product with literature data upon the authentic materials shown below (Sicher *et al.*, 1961; Tichy *et al.*, 1962; Sicher *et al.*, 1964):



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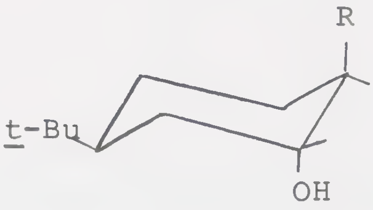


98

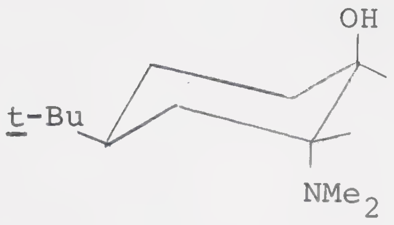
R	m.p. of (97)		m.p. of (98)
	Found	Reported	Reported
NH_2	109-109°	108.5-109.5°	98.5-99°
NH_2HCl	236-238°	239-240°	225-226°
NHTs	191°	192-193°	178-178.5°

The structure of the benzylaminoalcohol hydrochloride (96a) was confirmed by the mixed melting points of its debenzylated product and derivatives with those obtained from Sicher's pathway.

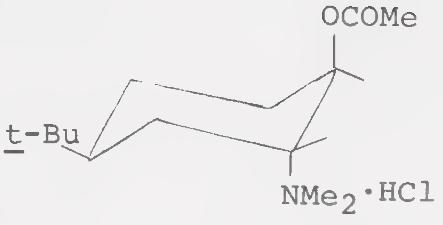
Isolation of the pure positional isomer (74a) was achieved more conveniently via crystallization of the N-tosyl derivatives than by use of the N-benzyl hydrochlorides.

The aminoalcohol (74a) was dimethylated in the presence of HCHO and HCO_2H and the N,N-dimethylated

product (75a) in crude form reacted with acetyl chloride to give the ester hydrochloride (99).

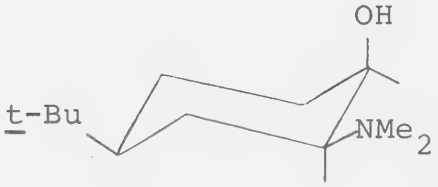


75a



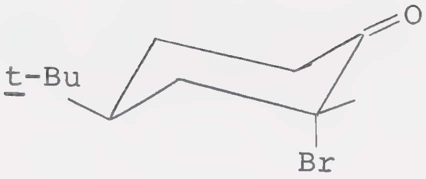
99

cis-2-Dimethylamino-4-*cis*-*t*-butylcyclohexanol ("O^a,N^e", 75b)



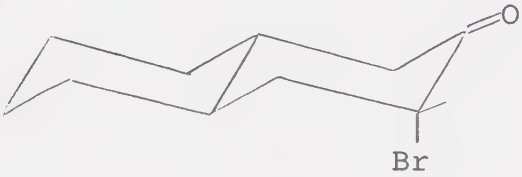
75b

The key material used to make *cis*-2-amino-*cis*-4-*t*-butylcyclohexanol (74b) or its N,N-dimethyl derivative (75b) was *trans*-2-bromo-4-*t*-butylcyclohexanone (100). In a literature survey on the synthesis of the *trans* bromo compound (100) and related compounds it was noticed that a 100% yield was claimed for a procedure employed by Smissman and his co-workers (1966) for



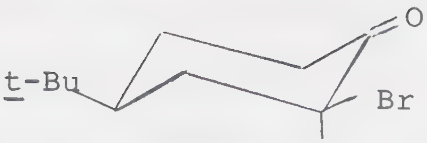
100

making pure 3(a)-bromo-trans-2-decalone (101); these



101

workers brominated 2-decalone with pyridinium hydrobromide perbromate. This process seemed more promising and less elaborate than that used By Allinger and Allinger (1958) to brominate 4-t-butylcyclohexanone; in the latter case, the bromination (by bromine) led to a cis and trans mixture (102 and 100) and the isolation of the trans isomer (100) was by way of a tedious chromatographic technique after fractional distillation of the cis isomer (102). Accordingly, the trans isomer (100) was prepared by bromination of 4-t-butylcyclohexanone with pyridinium hydrobromide perbromate. Both

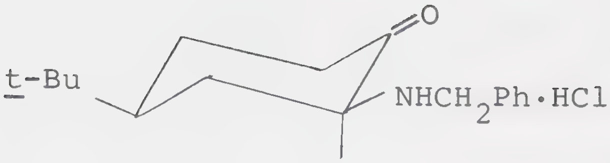


102

isomers were present in the total bromination product (total crude yield near 100%) as was evident from PMR data (see below). This result was different from the bromination of the decalone where only the trans isomer (101) was isolated (Smissman et al., 1966). The total distilled brominated product (yield, 80%) in CCl_4 showed two methine multiplets (centered at 255 and 272 Hz), that at higher field being assigned to the α-equatorial proton (W_H = 6.5 Hz) of the trans isomer (100) and that at lower field to the α-axial proton (W_H = 18 Hz) of the cis isomer (102) by comparison with reported data (Garbisch, 1964) and the isolated isomers in this work. The total distillate completely solidified when cooled in the refrigerator. This solid partially liquified at room temperature and collection of the residual solid by filtration and its crystallization from n-hexane gave 26% overall yield of the pure cis bromo isomer (102) which had a m.p., $\nu_{C=O}$ frequency and PMR methine

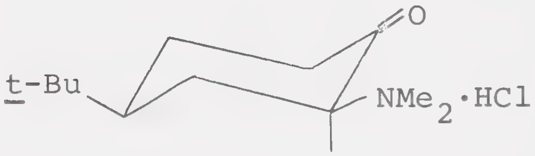
proton characteristics (discussed in the experimental) in agreement with literature data (Allinger and Allinger, 1958; Garbisch, 1964). The solidification and room temperature melting procedure was repeated several times, thus providing 52% overall yield the almost pure trans isomer (100) (traces of the cis isomer still remained, as shown by PMR spectrum) as the liquid fraction. The $\nu_{C=O}$ absorption of the trans isomer was at a lower wave number than that of the cis compound and consistent with the literature value (Allinger and Allinger, 1958). The so obtained trans isomer (100), without further purification, was used for the subsequent reactions.

An ethanol solution of the trans isomer (100) and benzylamine (ratio, 1:2) was heated under reflux in a nitrogen atmosphere; anhydrous ether was then added to the cooled reaction mixture to precipitate the hydrobromide salt of benzylamine. The mother liquid was treated with HCl-ethanol and then with anhydrous ether. The hydrochloride of the unreacted benzylamine separated first; this was separated and the residue from the filtrate refluxed with ethanol-HCl for 30 minutes, thus giving a hydrochloride in poor yield (5%) identified as (103). Its configuration was assigned as cis on the assumption that the reaction is of the S_N2 type (Smissman *et al.*, 1966); this assigned configuration was also confirmed by its PMR spectrum in



103

$CDCl_3$ where a broad signal (W_H = 20 Hz) centered at 218 Hz typical of axial-H was seen. Owing to the poor yield, the difficulty in getting a crystalline product and its instability, this route was abandoned, and the direct substitution of the bromine atom of (100) with dimethylamine under atmospheric pressure was investigated. The latter reaction in the presence of dry alcohol gave the desired product, isolated in the form of the hydrochloride salt (104), in good yield (70%); no reaction occurred when no solvent was used.

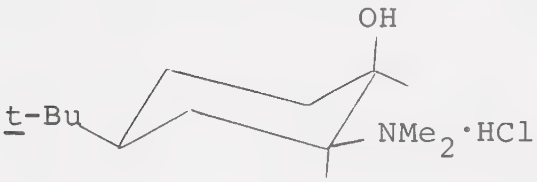


104

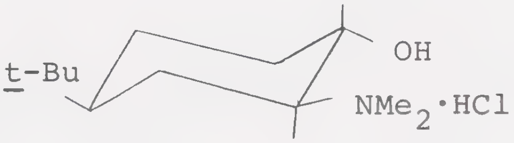
The configurational assignment to (104) was also based on PMR data, the spectrum of (104) in D_2O displaying

a broad signal (W_H = 26 Hz) centered at 254 Hz due to the α-methine proton.

Reduction of the ketone hydrochloride (104) in ethanol with hydrogen at atmospheric pressure and room temperature using platinum oxide as catalyst could not be brought to completion. The reduction mixture, after seven days treatment, was filtered. The residue from the filtrate showed a $\nu_{C=O}$ band of medium intensity corresponding with the starting ketone. Crystallization of this residue removed the ketone impurity (IR data) and the product appeared to be a mixture of the *cis* and *trans* aminoalcohols (105a and 105b) from its spectroscopic characteristics.

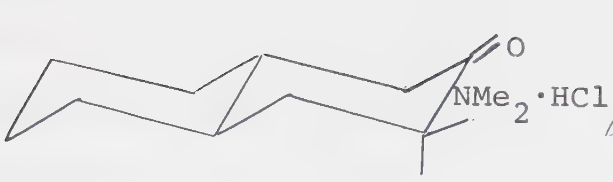


105a



105b

Its PMR spectrum showed two *t*-butyl singlets, one at 54 Hz (major one) and the other at 50 Hz (minor) in the ratio of about 3:1. Time did not permit further purification and characterization of these dimethylaminoalcohols. Smissman *et al*. (1966) reported that 3(e)-dimethyl-*trans*-decal-2-one hydrochloride (106) under the same conditions gave a single *cis* alcohol (107).



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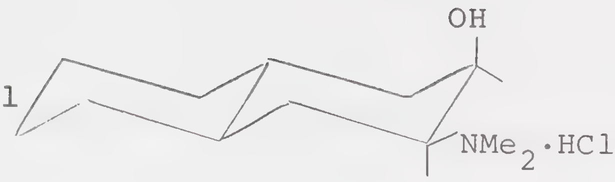
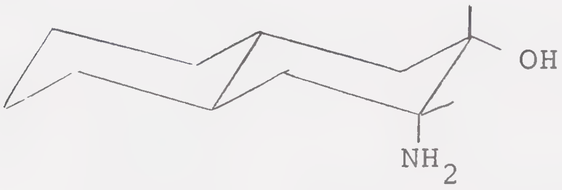


107

cis-2-Amino-trans-4-t-butylcyclohexanol ("O^e,N^a" 74c) and Its Derivatives

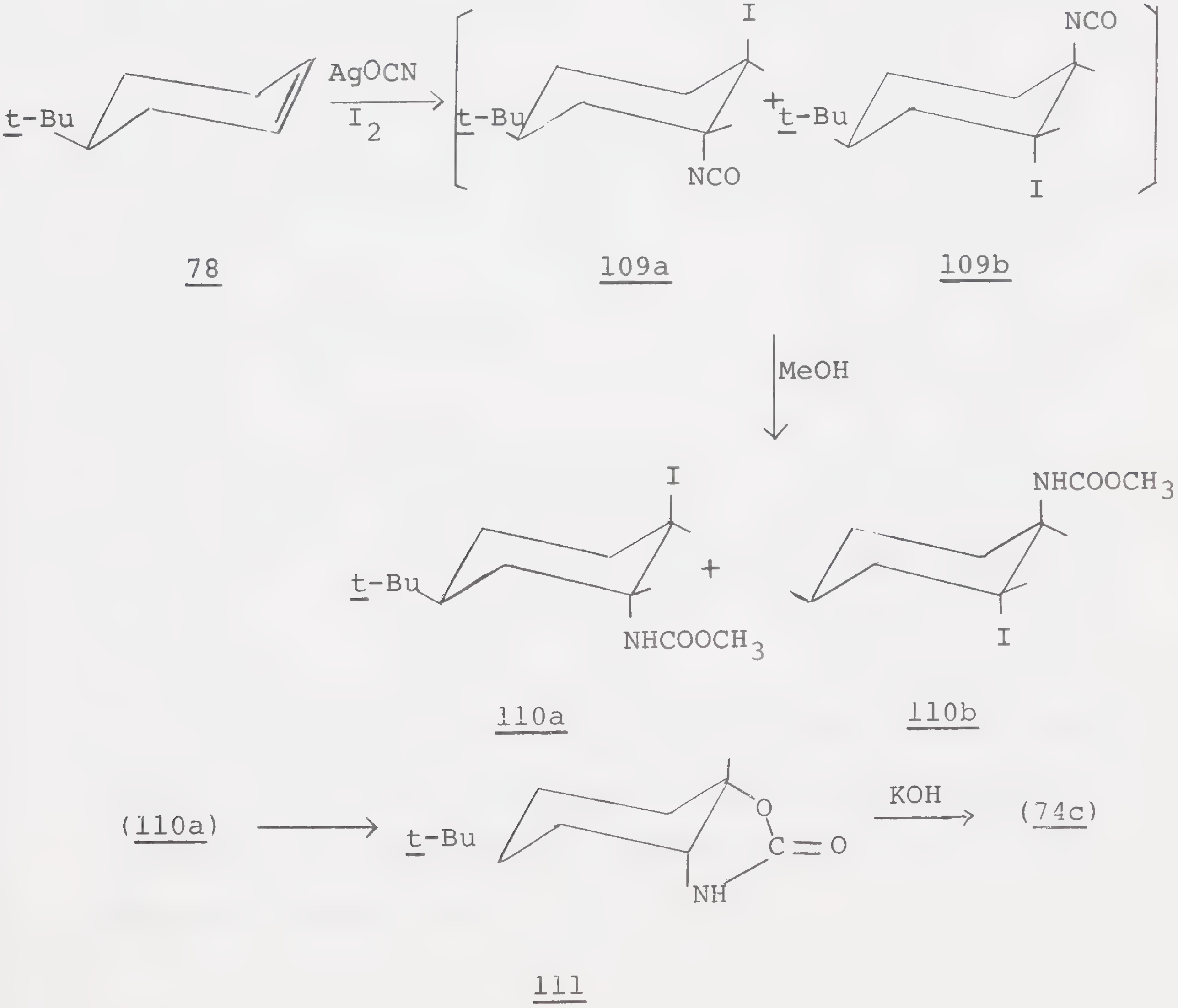
The reaction sequence used to synthesize 3(a)-amino-trans-2(e)-decalol (108) (Smissman et al., 1966) was



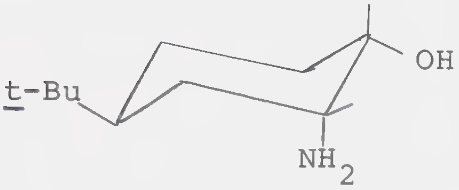
108

followed to make cis-2-amino-trans-4-t-butylcyclohexanol (74c). Addition of the iodoisocyanate anion to 4-t-butylcyclohexene (78) and the subsequent methanolysis of the iodoisocyanates (109a and 109b) thus formed afforded a mixture of positional isomers, (110a) and (110b) (the reaction scheme shown below), the PMR spectrum ($CDCl_3$) of which displayed two singlets (54 Hz and 64 Hz) of equal

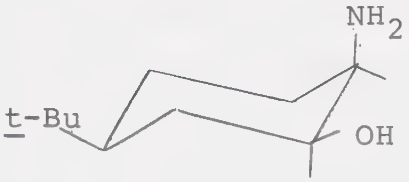
intensities due to the t-butyl groups of the two isomers (no vinylic signal was seen). Addition of this pseudohalogen has been demonstrated to occur in a diaxial manner (Hassner and Heathcock, 1964). The product (110a) which crystallized first from methanol had a t-butyl singlet at 54 Hz, and was subjected to pyrolysis to yield the corresponding cyclic urethane (111). Alkaline hydrolysis of the urethane provided the amino alcohol (74c). The



structure of the product (*74c*) was identified by observing mixed melting points with authentic *cis*-2-amino-*trans*-4-*t*-butylcyclohexanol (no depression) and *cis*-2-amino-*cis*-5-*t*-butylcyclohexanol (*112*) (depression, 85-86°) (these samples were kindly given by Dr. J. Sicher) and by comparing the melting points of this isomer (*74c*) and its hydrochloride with literature data (Sicher *et al*., 1961; Tichý *et al*., 1962; Sicher *et al*., 1964) as illustrated below:



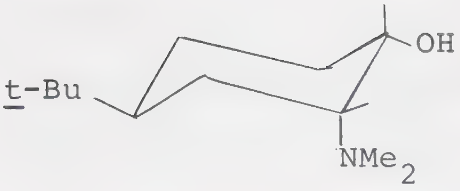
74c



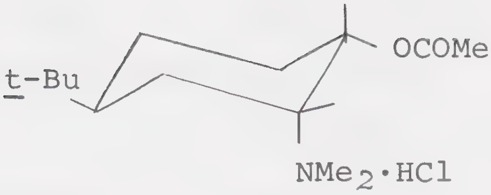
112

	m.p. of (*74c*)		m.p. of (*112*)
	Reported	Found	Reported
free base	112-113°	112-113°	110.5-111°
HCl	249-250°	242-244°	226-228° (½ H_2O)

The aminoalcohol (*74c*) was converted by the Leukart reaction ($HCHO-HCO_2H$) into the N,N-dimethylated compound (*75c*) which was acetylated with acetyl chloride to give the ester hydrochloride (*113*).



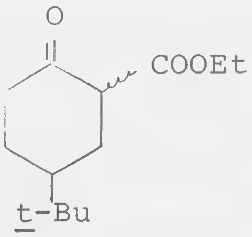
75c



113

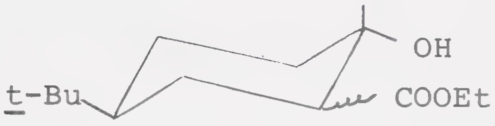
trans-2-Amino-trans-4-t-butylcyclohexanol ("O^e,N^e", 74d)

Carboxylation of 4-t-butylcyclohexanone in the presence of triphenylmethyl potassium to produce the corresponding ketone acid (87) was attempted by Sicher et al.'s procedure (1961), but the starting material was recovered. This failure prompted the use of the alternative synthetic pathway, namely, carbethoxylation (Krapcho et al., 1967). Reaction of 4-t-butylcyclohexanone with diethylcarbonate in the presence of sodium hydride gave an isomeric mixture of the corresponding keto esters (114) in 71% yield. The



114

keto esters thus formed were reduced with sodium borohydride to the hydroxy esters (115) which equilibrated to *trans*-2-hydroxy-*cis*-5-*t*-butylcyclohexanecarboxylic acid (85) in the presence of sodium methoxide. This acid was a solid with a m.p. corresponding with the reported value. It was subjected to the sequence (as illustrated below) following the procedure of Sicher *et al.* (1961). Each step proceeded well and physical data consistent with literature values were obtained. Time did not allow conversion of the aminoalcohol (74d) to the Ach analog (73d).



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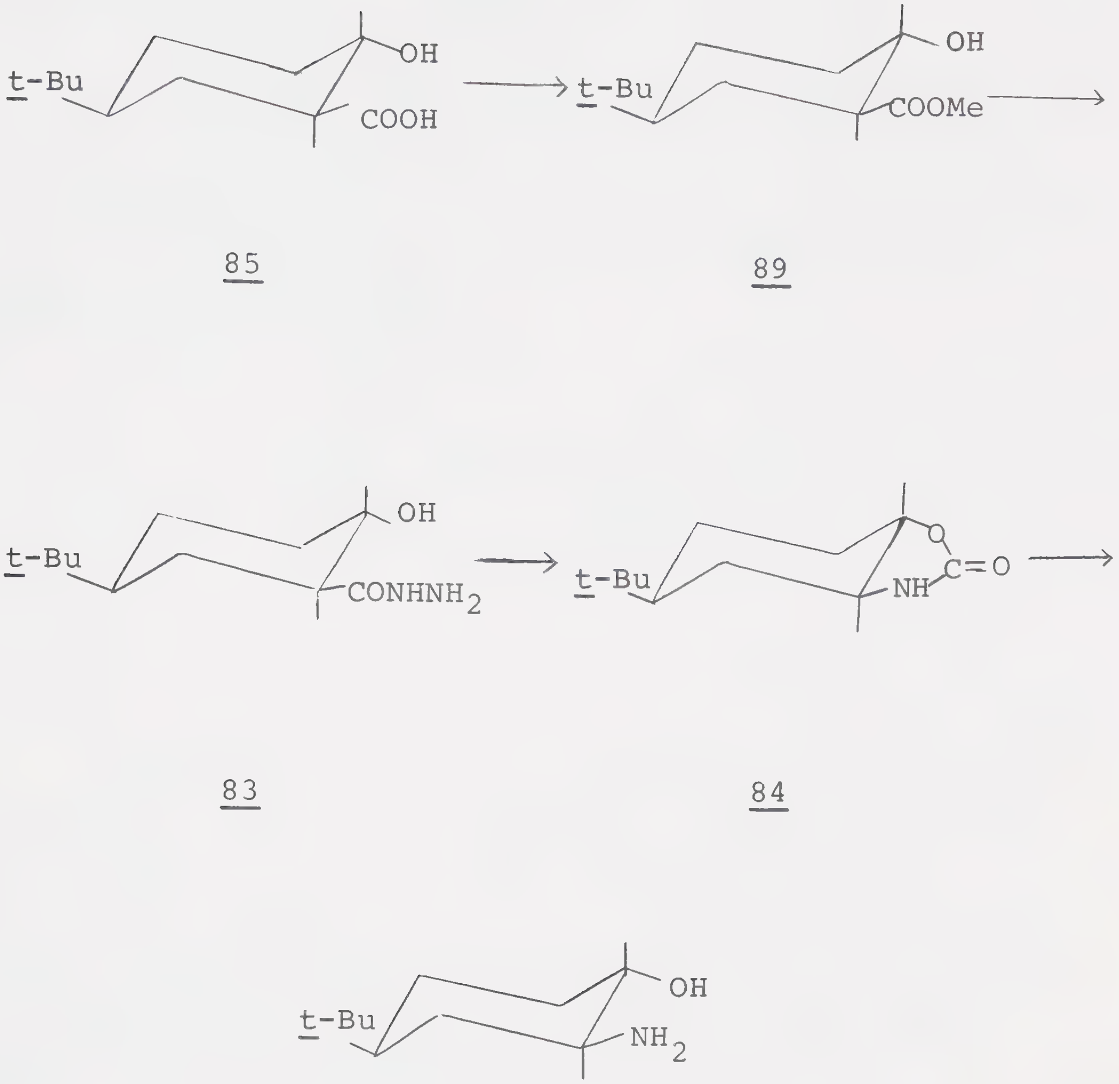
Note

Although none of the required *t*-butylcyclohexane Ach analogs could be obtained in the time available, the synthetic route for each isomer has been established. It is anticipated that the completion of this project may now be accomplished without difficulty.



85

89

83

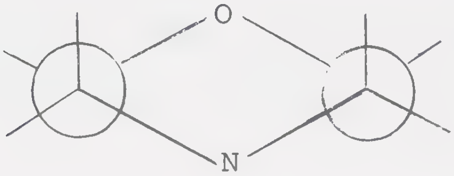
84

74d

iv) MORPHOLINE DERIVATIVES

This series was prepared for two reasons.

1) The provision of model PMR spectra typical of NCCO *gauche* system. In the morpholine ring the nitrogen and oxygen atoms are, of necessity, confined in a *gauche* relationship (116).

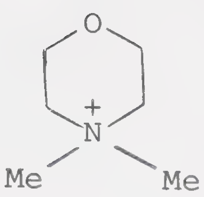


116

2) For pharmacological evaluation. The presence or absence of muscarinic properties in these model compounds would provide valuable information upon the "active" Ach conformation. Some morpholine derivatives have already been examined as muscarinic agents and several were significantly active (Waser, 1961).

Synthesis

N-Methylation of morpholine with formaldehyde-formic acid and the subsequent quaternization of the thus formed N-methylated compound, N-methylmorpholine, with methyl iodide and benzyl bromide afforded N,N-dimethylmorpholinium iodide (117) and N-benzyl-N-methylmorpholinium bromide (118) respectively.



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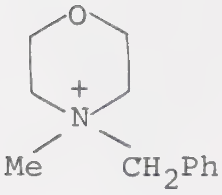

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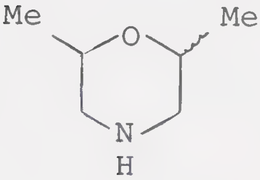
Commercial 2,6-dimethylmorpholine (119), composed of a mixture of the *cis* and *trans* isomers (119a and 119b) with a ratio of ca. 3:1 respectively (from PMR integral data), was



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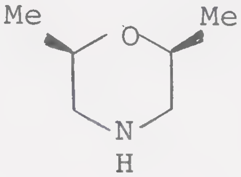
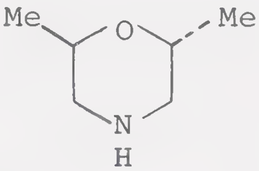
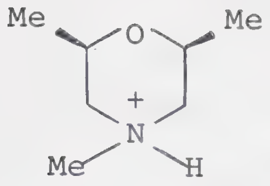


119a

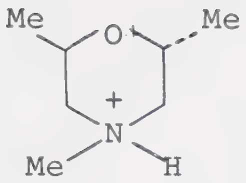


119b

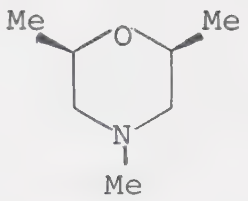
N-methylated and then reacted with hydrochloric acid, the *cis* hydrochloride (120a) being obtained by fractional crystallization from ethanol-ether in 85% yield (its structural assignment follows later). Attempts to isolate the pure *trans* isomer (120b) by fractional crystallization were not successful, but a mixture richer in the *trans* isomer was obtained.



120a

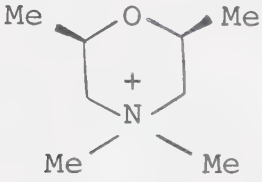


120b

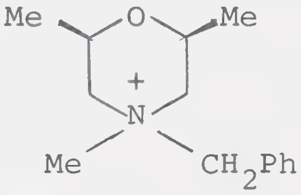


121

The pure cis N-methylated base (121), obtained by treating the cis hydrochloride with sodium hydroxide, was quaternized with methyl iodide and benzyl chloride

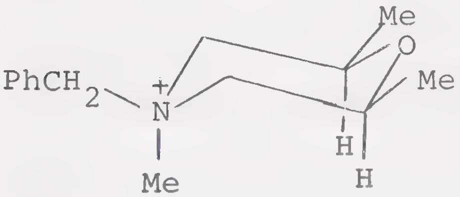


122

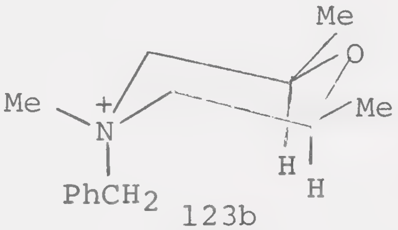


123

to yield the corresponding methiodide (122) and benzyl salt (123), the latter having two isomeric forms α (123a) and β (123b) (the configurational assignment is discussed



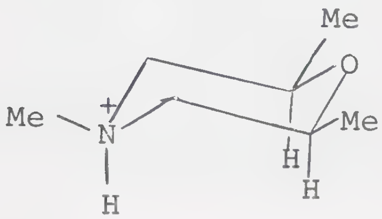
123a



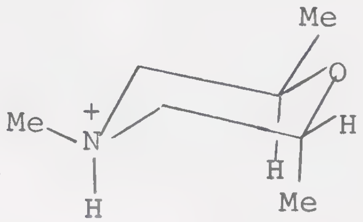
123b

later). The two benzyl isomers were separated from an alcohol-ether mixture by fractional crystallization and the yield of the pure α- and β-isomers isolated were 23% and 8% respectively.

The configurational assignment of the *cis* hydrochloride (120a) is based on the following argument. The preferred conformations of the *cis* and *trans* isomers are (120a') and (120b') respectively. In (120a') the 2- and 6-Me PMR signals will be identical but in (120b') they should differ because one methyl group has an axial and the other an equatorial environment (in the free base an averaged environment results since the axial 2-Me conformer population equals that of the equatorial 2-Me form). In fact, the 2- and 6-Me PMR signal of the *cis* hydrochloride was a single doublet while that of the *trans* isomer was two doublets, confirming the stereochemical assignments. The lower field C-Me signal of the *trans* salt is attributed to the axial methyl group because this is more subject to the deshielding influence of the protonated nitrogen atom (Casy, 1966).



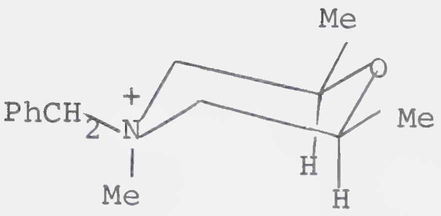
120a'



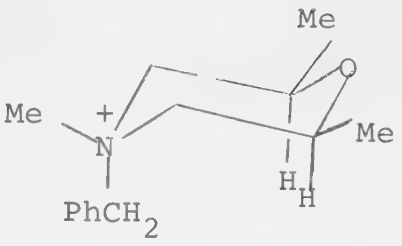
120b'

The assignment of the configurations to the α- and β-isomers of the benzyl derivative (123) is made on the basis of the resonance signals of the benzylic methylene, the 2- and 6-Me and the NMe protons in their PMR spectra in D_2O as illustrated below (detailed PMR signals

are given in experimental):



α-isomer (123a)



β-isomer (123b)

PMR signal	α-isomer	β-isomer
PhCH$_2$	286 Hz	276 Hz
NMe	184 Hz	190 Hz
2- and 6-Me	79 Hz	76 Hz

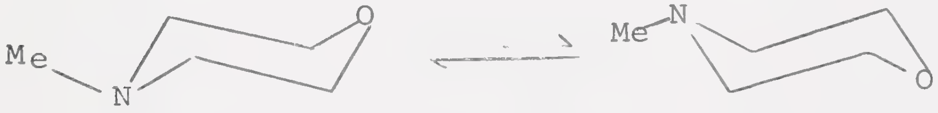
The known fact that axial substituents in the cyclohexane ring or related systems are usually more shielded than equatorial ones (Jackman, 1959) makes reasonable the assignment that the α-isomer (123a) has an equatorial benzyl group and the β-isomer (123b) an axial benzyl group, since the benzylic methylene singlet in the α-isomer (at 286 Hz from DSS) is down field of that in the β-isomer (at 276 Hz). Further evidence in support is the higher field NMe singlet (184 Hz) found in the α-isomer (β-NMe signal is at 190 Hz). Brown and his colleagues (1967) have employed similar arguments in the case of related quaternary piperidine derivatives.

The 2- and 6-Me groups in the β-isomer appear to be slightly shielded by the benzyl function, since the

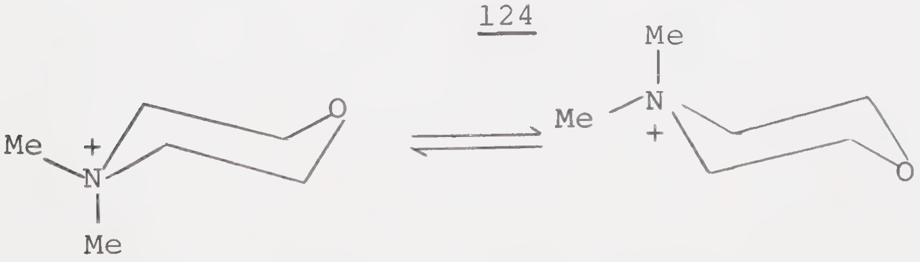
PMR signal of these groups is higher field than the corresponding resonance in the α-isomer. The benzyl group should not influence the 2- and 6-Me groups in the α-isomer because it is too far away (the 2,6-methine signal is also higher field in the β-isomer).

PMR Characteristics of Morpholine Derivatives in Relation to Those of Acetylcholine

The methylene ring proton PMR signals of N-methylmorpholine and N,N-dimethylmorpholinium iodide (117) closely resemble those of Ach. In the free base (Figure 5c in Chapter IV) both NCH_2 and OCH_2 signals appear as multiplets with the typical pattern of the $\overset{+}{N}CH_2$ signal of Ach and its congeners; in the quaternary salt (117) the OCH_2 multiplet was broadened (as in that of Ach) by $\overset{+}{N}CCH$ coupling. Both morpholine derivatives could be analyzed as A_2B_2 systems (Smith and Shoulders, 1965) because equivalence of the chair conformers (124, 125)



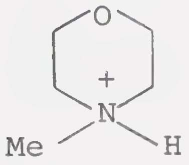
124



125

renders the NCH_2 and OCH_2 protons equivalent. These data thus support the interpretation of the Ach spectrum in terms of a *gauche* $\overset{+}{N}CCO$ conformation (see Chapter IV).

Ring methylene spectral characteristics of the derivatives (126, 118) are far more complex. In these cases marked conformational preferences exist, hence the protons represent an ABCD rather than A_2B_2 system.



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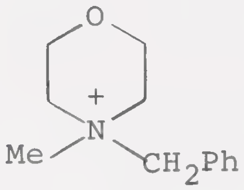


118

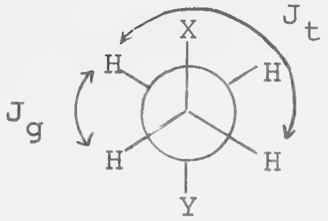
CHAPTER IV

SPECTROSCOPIC STUDIES OF ACETYLCHOLINE, ITS ANALOGS AND RELATED COMPOUNDS

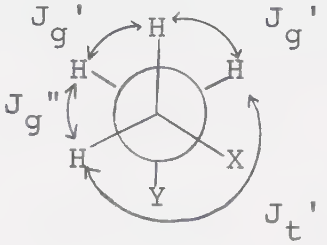
i) PMR STUDIES

The PMR analysis of Ach reported by Culvenor and Ham (1966) is outlined below, after some general remarks upon A_2B_2 (A_2 X_2) spin-spin coupled systems.

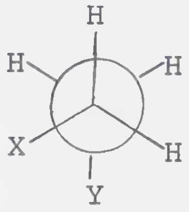
There are three possible staggered conformers for molecules of type XCH_2CH_2Y, one trans (127a) and two equivalent gauche forms (127b, 127c). In each conformer



127a



127b



127c

at least two distinct vicinal coupling constants are involved; thus in (127a) there are one J trans (J_t) and one J gauche (J_g), and in (127b) one J_t and three J_g couplings. Rapid interconversion of conformers by rotation about the C-C bond renders each geminal pair of protons chemically equivalent and the four proton system is described as A_2X_2 or A_2B_2 depending on whether the chemical shift difference between the methylene pairs is large or small. The same rotation does not, however, lead to a single, averaged vicinal coupling constant

except when the conformer populations are equal. Hence, spectra obtained are complex and cannot be analyzed by a first order treatment. The detailed analysis of these systems is outside the scope of this thesis, but certain features are summarized below.

A_2B_2 (and A_2X_2) systems give spectral patterns which are symmetrical about their midpoints; one half is due to the A_2 and the other to the $B_2(X_2)$ group and either may be used for spectral analysis. In the most general case, four coupling constants are involved

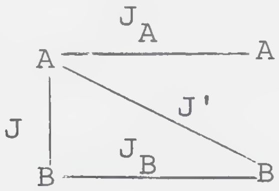


FIGURE 3. Diagrammatic representation of couplings in A_2B_2 system.

(Figure 3). These may not be derived directly from the spectrum but may be calculated in terms of the parameters:

$$K = J_A + J_B; \quad L = J - J'$$

$$M = J_A - J_B; \quad N = J + J'$$

In most cases $J_A = J_B$ and $M = 0$.

In principle, an A_2B_2 system gives rise to twelve transitions per group (i.e. 24 transitions in all) but in practice, fewer lines are generally observed (Figure 4a, 4b). A strong doublet is usually discernable formed from lines 1, 2 and 3, 4 and the distance between lines

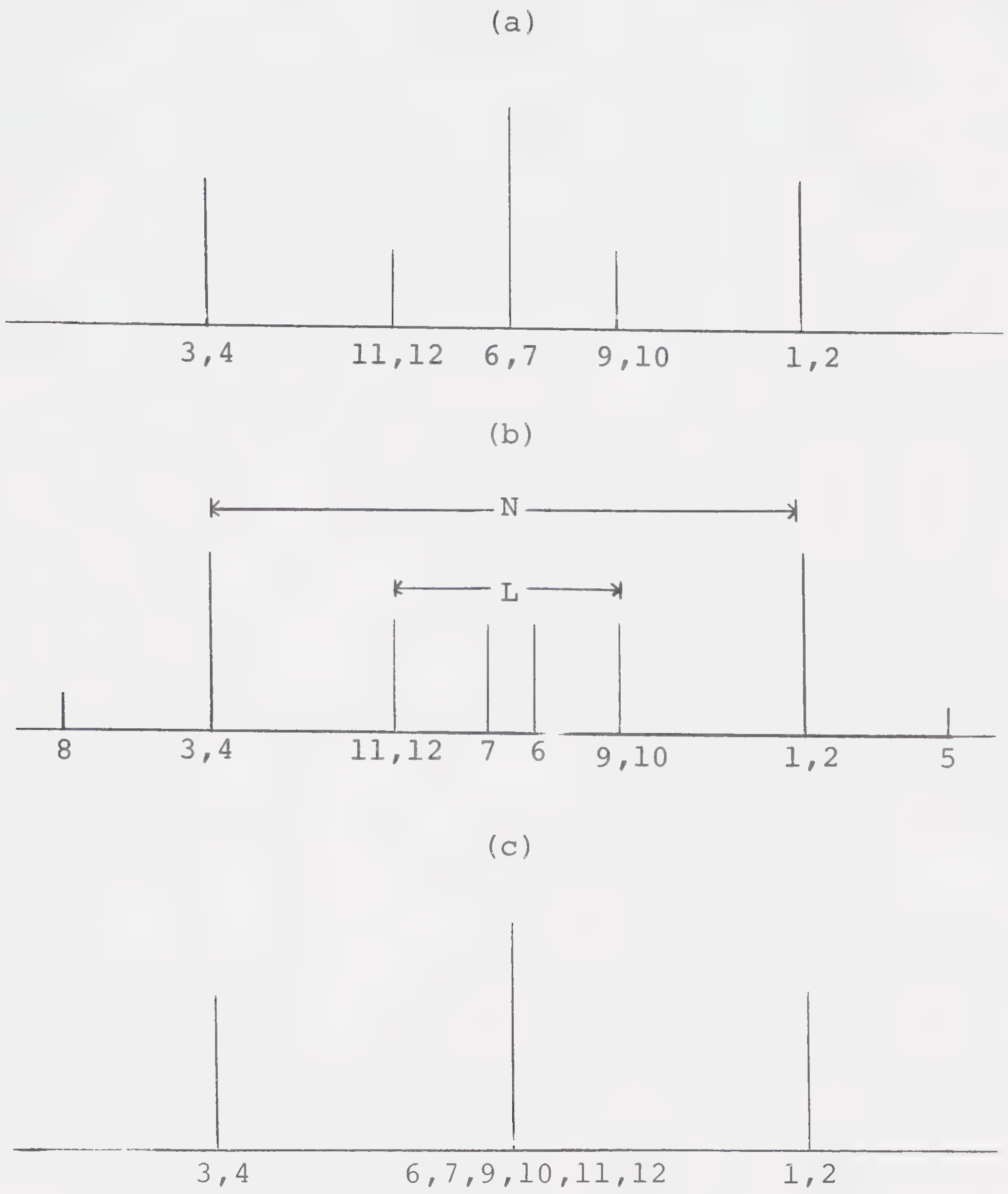


FIGURE 4. Diagrammatic representation of the A_2 portion of A_2B_2 PMR spectra (Sheppard and Turner, 1959) with M=0 and

(a) $L \neq 0$, $N=3L$, $K \gg L$ or N;

(b) $L \neq 0$, $N=3L$, $K=3L$;

(c) $L=0$

gives the sum of coupling constants (N). The distance between lines 11 and 10 gives an approximate value for the magnitude (but not the sign) of the difference between J and J' (L). If N and L are known, the values J and J' follow since N + L = 2J. When J and J' are equal (L=O), a triplet is obtained (Figure 4c).

Culvenor and Ham's treatment (1966) of the spectrum of Ach may now be discussed. Part of the 60 MHz spectrum of Ach chloride in D_2O is shown in Figure 5a. The lower field multiplet due to the OCH_2 protons is broader than the $\overset{+}{N}CH_2$ multiplet because of an additional coupling of about 2 Hz between CH_2O and the positively charged nitrogen atom (nuclear spin 1). In quaternary nitrogen salts the three bond NCCH coupling is known to be larger (1.5-2 Hz) than the 2 bond NCH coupling (0-0.6 Hz) (Meiboom, 1957; Anderson et al., 1963; LaLancette and Benson, 1963; Binsch et al., 1964). N and L values were estimated as shown from the high field multiplet (Figure 4b) and refined by means of an iterative calculation and computer program, giving N, 9.49 Hz and L, 4.43 Hz; the two vicinal J values are therefore 7.0 and 2.5 Hz. Anticipated values are as follows:

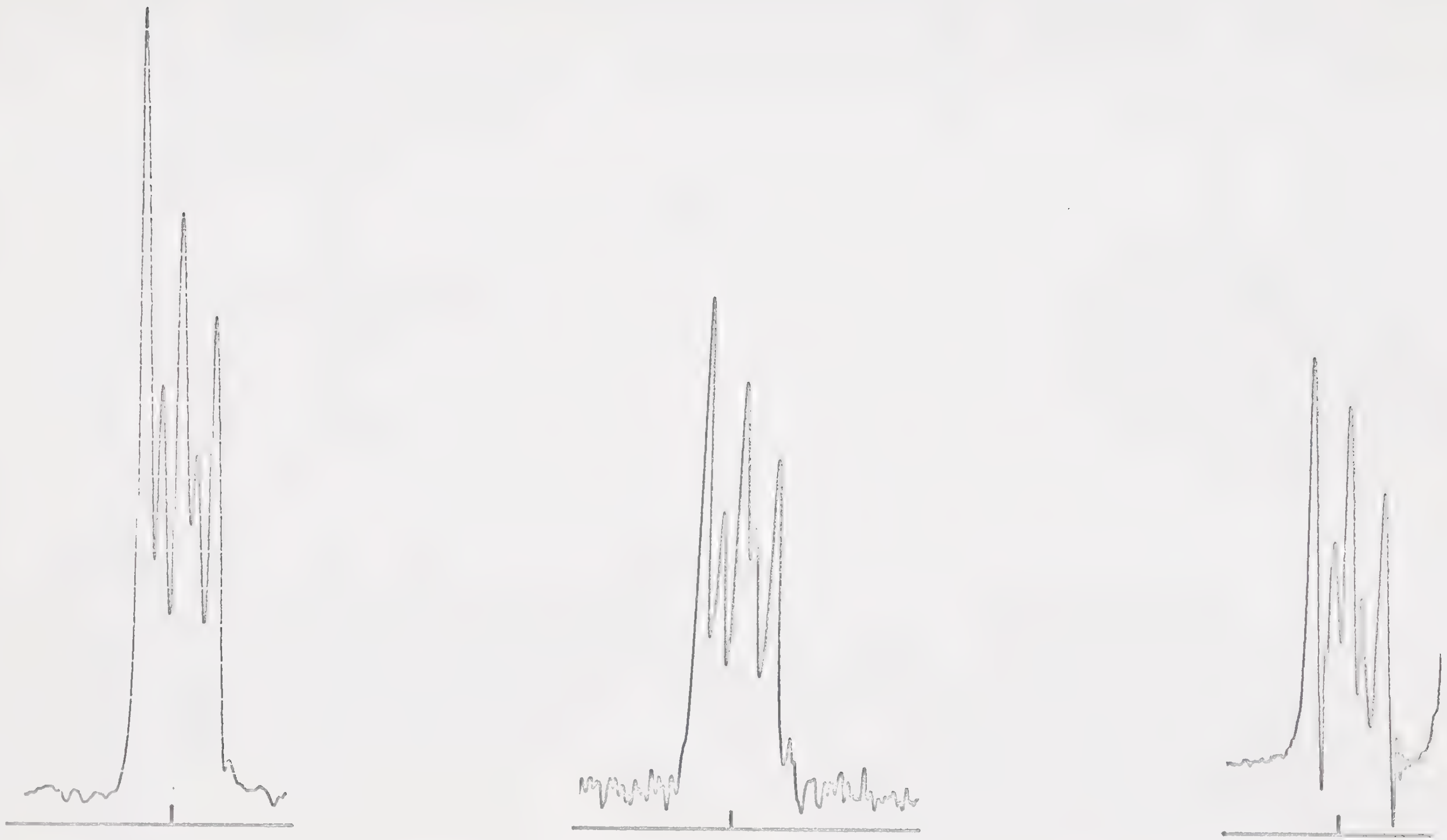
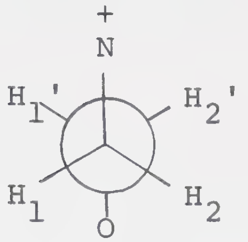


FIGURE 5. NCH$_2$ PMR signals in D$_2$O of Ach (a), (β-acetoxyethyl)benzyldimethylammonium bromide (b) and N-methylmorpholine (c). Recorded at 60 MHz.

a) trans conformer favored.

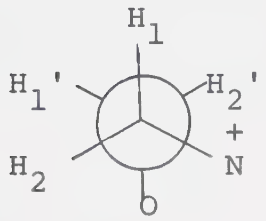


128a

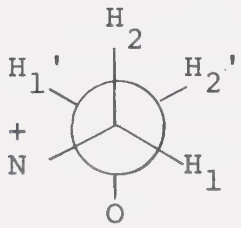
$$J_{11'} = J_g$$
$$J_{12'} = J_t$$

In this case the smaller coupling (2.5 Hz) could correspond with J_g, but the larger value (7.0 Hz) is abnormally low for J_t even allowing for substituent effects.

b) gauche conformers favoured.



128b



128c

$$J_{11'} = \tfrac{1}{2}\,(J_g + J_t)$$
$$J_{12'} = \tfrac{1}{2}\,(J_g + J_g) = J_g$$

Here the 2.5 Hz coupling is consistent with the J_g value whereas J = 7.0 Hz approaches the expected value of $\tfrac{1}{2}\,(J_t + J_g)$, e.g. about (10 + 3)/2 = 6.5 Hz. On this basis J_t has a value (11.5 Hz) within the normal range.

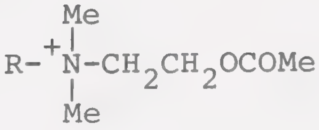
Thus PMR evidence favors a high proportion of an Ach conformation which is gauche about the $\overset{+}{N}CCO$ bond.

In view of the bulk of the $\overset{+}{N}Me_3$ substituent, this

result is surprising since steric interactions between the N and O substituents will clearly be less in the trans conformer.

The spectral appearance of the NCH_2 proton signal showed little variation when D_2O was replaced by DMSO-d_6 or $CDCl_3$ (Table 3, No. 1) and D_2O-pyridine or trifluoracetic acid (Culvenor and Ham, 1966), hence conformer population appears to be little influenced by solvent.

It was of interest to examine the PMR spectra of Ach analogs in which the quaternary nitrogen group was even larger than $\overset{+}{N}Me_3$ to see if preference for *gauche* conformers be maintained when the destabilizing steric factor is increased. To this end the spectra of the derivatives of type (12) were recorded in D_2O (synthesis described earlier). Spectral characteristics are given in Table 3.



$$R-\overset{+}{N}(Me)_2-CH_2CH_2OCOMe$$

12

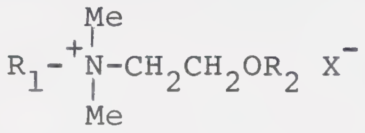
R = - $CH_2CH=CH_2$ 13

- CH_2Ph 14

- $CHMe_2$ 15

- *t*-Bu 16

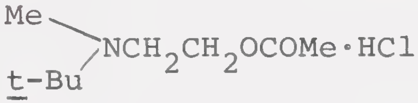
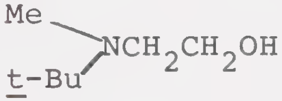
TABLE 3. PMR CHARACTERISTICS OF COMPOUNDS OF TYPE XCH_2CH_2Y



$$R_1-\overset{+}{N}(Me)_2-CH_2CH_2OR_2\ X^-$$

No.	R_1	R_2	X	PMR Signals[a]		Solvent
				OCH_2[b]	NCH_2[b] (N;L)[c]	
1	Me	COMe	Cl	275[d]	225 (9.5; 5)	D_2O
				265	228 (9.5; 5)	DMSO-d_6
				274	248 (9.5;4.8)	$CDCl_3$
2	Me	H	Cl	240	211 (10; 5)	D_2O
3	CH_2=$CHCH_2$	COMe	Br	272[d]	221 (9.8;4.8)	D_2O
4	CH_2=$CHCH_2$	H	Br	e	209 (10; 5)	D_2O
5	$PhCH_2$	COMe	Br	277	225 (10; 4.5)	D_2O
				281	252 (10; 5.8)	$CDCl_3$
6	$PhCH_2$	H	Br	248	211 (10; 5)	D_2O
7	Me_2CH	COMe	Br	d	223 (10; 4)	D_2O
8	Me_2CH	H	Br	f	209 (9.5; 4)	D_2O
9	_t_-Bu	COMe	I	274[d]	220 (10; 4)	D_2O
10	_t_-Bu	H	I	245	206 (10; 4)	D_2O

TABLE 3 continued

No.	Full Structure	PMR signals[a]		Solvent
		OCH_2[b]	NCH_2[b] (N;L)[c]	
11	$Me_3CCH_2CH_2OH$	216 (triplet;Δ=8)	88 (triplet;Δ=8)	CCl_4
12	$Me_3CCH_2CH_2OCOMe$	243 (triplet;Δ=7)	91 (triplet;Δ=7)	CCl_4
13	$Me_2NCH_2CH_2OCOMe\cdot HCl$	267	210 (10;3.8)	D_2O
14	 $(Me)(t\text{-}Bu)NCH_2CH_2OCOMe\cdot HCl$	257	g	D_2O
15	$NH_2CH_2CH_2OCOMe\cdot HCl$	252	201 (10, 5)	D_2O
16	$Me_2NCH_2CH_2OH$	219.5 (triplet;Δ=6)	149 (triplet;Δ=6)	D_2O
17	$Me_2NCH_2CH_2OCOMe$	151 (triplet;Δ=5)	160 (triplet;Δ=5)	D_2O
18	 $(Me)(t\text{-}Bu)NCH_2CH_2OH$	212 (triplet;Δ=5.5)	153 (triplet;Δ=5.5)	$CDCl_3$
19	$Me_3\overset{+}{N}CH_2CH_2SCOMe\ Cl^-$	202[h]		

[a] All data were recorded on a Varian A-60D at the normal operating temperature. Chemical shifts in Hz from TMS are given. Separations (Δ) of triplets are also given.

Continued

TABLE 3 continued

[b] Centres of multiplets are given.

[c] N and L values were measured on the basis of Culvenor and Hams' treatment (1966) when possible and these values are approximate.

[d] Overlapping with water peak.

[e] Obscured by $\overset{+}{N}\underline{CH}_2CH{=}CH_2$.

[f] Obscured by $\overset{+}{N}\underline{CH}Me$.

[g] Broad and complicated signal.

[h] Two methylene signals overlap each other.

1. (β-Acetoxyethyl)allyldimethylammonium Bromide (13)

The PMR spectrum of (13) (Table 3, No. 3) in D_2O showed methylene signals similar to those in the Ach spectrum. In the spectrum of the corresponding alcohol quaternary salt (129) (Table 3, No. 4), the methylene multiplet of NCH_2 looked closely like that in the spectrum of Ach and imitated that in the choline spectrum (Table 3, No. 2), the latter showing methylene multiplets similar to Ach signals (Culvenor and Ham, 1966); the OCH_2 signals was obscured by the presence of a doublet due to the methylene protons of $\overset{+}{N}\underline{CH_2}CH{=}CH_2$.

2. (β-Acetoxyethyl)benzyldimethylammonium Bromide (14)

The NCH_2 signal of Ach was reproduced in the spectrum of (14) in D_2O (Figure 5b) (Table 3, No. 5). The OCH_2 multiplet could not be clearly seen as a result of overlap with water peak. The two methylene signals in the spectrum of (14) in $CDCl_3$ had the same patterns as those of the Ach spectrum in $CDCl_3$.

The two methylene resonances in the spectrum of the alcohol quaternary salt (19) (Table 3, No. 6) showed usual Ach-like signals with slight modification of the NCH_2 multiplet and imitated those in the choline spectrum.

3. (β-Acetoxyethyl)dimethylisopropylammonium Bromide (15)

The NCH_2 signal in the spectrum of (15) (Table 3,

No. 7) overlapped another proton signal ($-\overset{+}{N}\underline{CH}Me_2$), but the usual Ach $N\underline{CH}_2$ pattern could be observed. The NCH_2 signal, which resembled that in the choline spectrum, was also seen in the corresponding alcohol quaternary salt (20) (Table 2, No. 8).

The $NCH\underline{Me}_2$ signal of the acetate (15) was a broad doublet due to the long range coupling influence of nitrogen. This coupling of the NCCH type was supported by the observation of two clear doublets of triplets with J = 1.5 Hz ($NCH\underline{Me}_2$ signal) in the spectrum of the corresponding alcohol (20).

4. (β-Acetoxyethyl)-*t*-butyldimethylammonium Bromide (16)

The usual NCH_2 signal of Ach was shown in the spectrum of (16) (Table 3, No. 9) in D_2O and the OCH_2 signal overlapped the water peak. The two methylene multiplets in the spectrum of the corresponding alcohol quaternary salt (21) (Table 3, No. 10) were very similar to those in the Ach spectrum.

In the spectrum of 2-(N-*t*-butyl-N-methylamino)-ethanol (22) in $CDCl_3$, the presence of two triplets (peak separation = 5.5 Hz), assigned to the two methylene groups, leads to the conclusion that there is no conformational preference in this compound (for detailed discussion see 3,3-dimethyl-*n*-butyl acetate). The two methylene signals in the alcohol (22) hydrochloride in

$CDCl_3$ were difficult to resolve and could not be used to aid this present discussion.

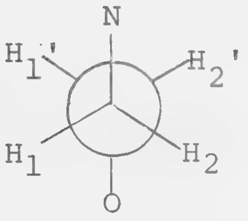
It was noticed that t-butyl singlet was a broad signal in the spectrum of the acetate quaternary salt (16) while a t-butyl triplet with J = 1.5 Hz was found in the spectrum of the alcohol quaternary salt (21). Again, this is another example of NCCH coupling.

From these results, it is clear that the methylene proton PMR characteristics of the Ach analogs (13, 14, 15, 16) clearly resemble those of Ach itself (see especially NCH_2 signals in Table 3). These data, following the analysis of Culvenor and Ham (1966), thus support preferred *gauche* conformers for the analogs (13, 14, 15, 16) in D_2O and show that replacement of one of the NMe groups of Ach by a bulkier group has no significant effect upon the conformational equilibrium of this class of compounds.

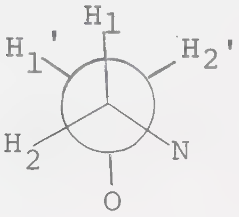
PMR results upon 3,3-dimethyl-n-butanol and its esters (27) (the ester is termed carbocholine) (Table 3, No. 11, 12) establish that the bulky substituent must carry a positive charge in order that *gauche* conformers be preferred in these β-substituted ethanol derivatives. Thus the methylene PMR signals of both the free alcohol and the ester in CCl_4 appeared as almost symmetrical triplets characteristic of an absence of conformational preference (Whitesides *et al*., 1967).

Note:

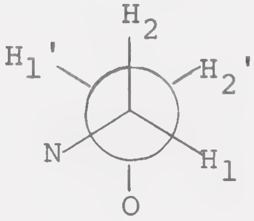
If the population of conformers (130a), (130b) and (130c) be equal, the average H_1/H_1' coupling constant $(J_g + J_g + J_t)/3$ is equal to the average H_1/H_2' coupling, hence the H_1 (and H_1') signal will appear as a 1:2:1 symmetrical triplet with $J = (J_g + J_g + J_t)/3$ (Whitesides et al., 1967).



130a



130b



130c

Conformational preferences in Ach analogs do not require a quaternary charged center since the PMR methylene characteristics of 2-dimethylaminoethyl acetate hydrochloride (Table 3, No. 13) are similar to those of the quaternary salts (Table 3).

The methylene signals of the primary aminoester hydrochloride (26) also suggest preference for gauche N/O conformers (Table 3, No. 15).

All free bases examined however had methylene proton PMR features typical of a lack of conformational preference (Table 3, No. 16, 17).

PMR data upon free alcohol quaternary salts (19, 20, 21, 129) typified by choline (Table 3, No. 2) support conformational preferences as seen for the acetate of these alcohols. Thus the alcoholic oxygen, rather than the entire acyloxy group, appears to be the important feature influencing the conformation of these compounds.

When the oxygen is replaced by sulfur as in acetylthiocholine (131), the methylene PMR signals are markedly different from those of Ach and its analogs. The NCH_2

$$Me_3\overset{+}{N}CH_2CH_2SCOMe$$

and SCH_2 signals are much closer together (Fig. 6) and form a multiplet approximately symmetrical about the mid point. No clear assignment of L and N values is possible. This result indicates that conformational preferences in the thio derivative are different from those in Ach and its congeners as mentioned before. It is significant in this respect that X-ray analysis of acetylthiocholine shows that the crystalline salt has a *trans* N/S conformation (Sundaralingam, 1968).

In summary, this PMR study shows that *gauche* N/O conformers are favored in Ach and related compounds and that this conformational preference depends on the presence in the molecule of a charged nitrogen atom three bonds removed from oxygen.

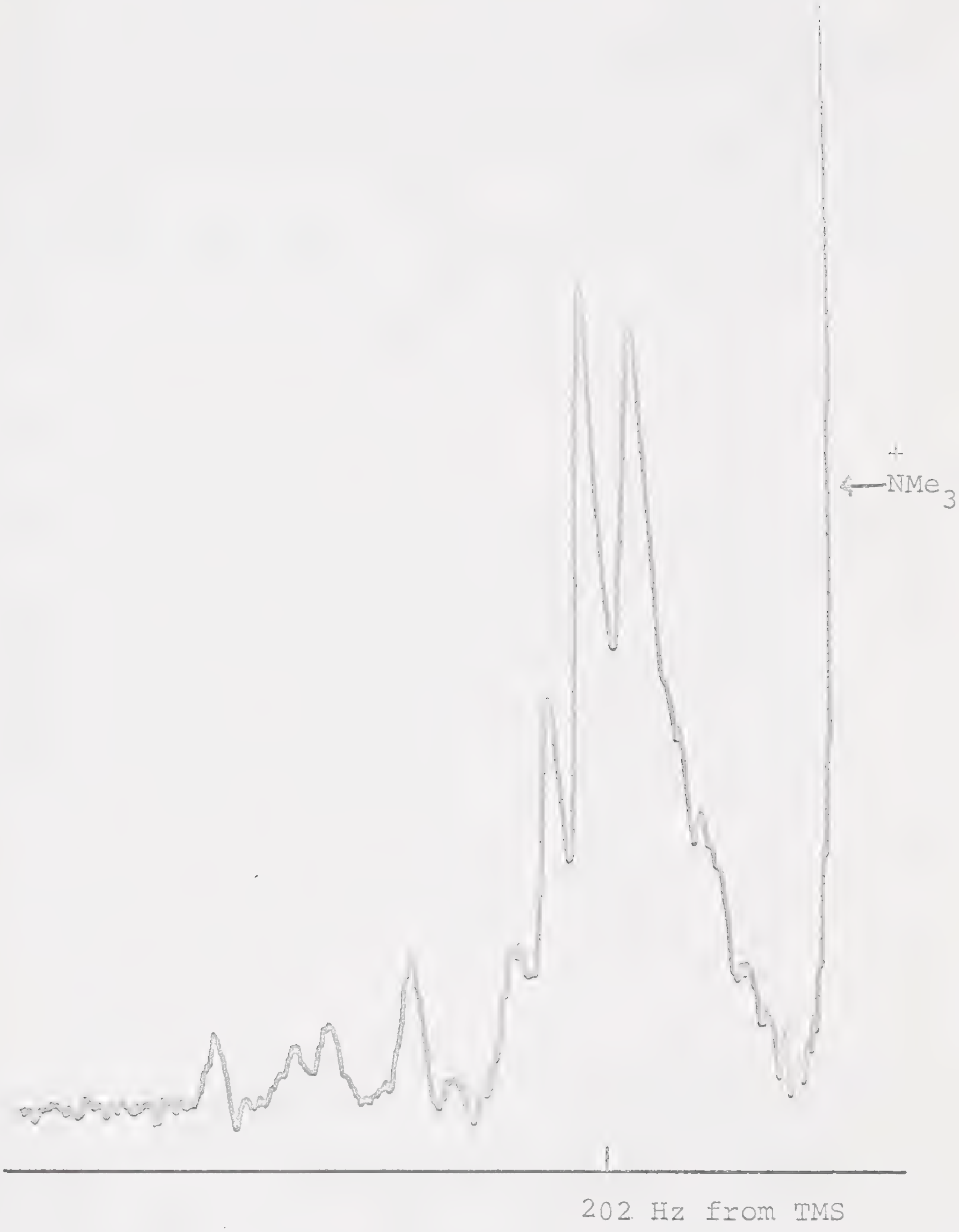
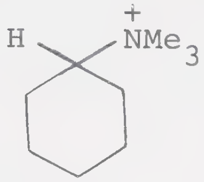


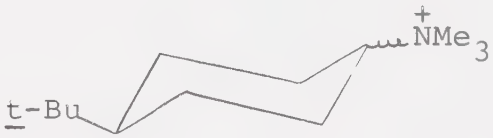
FIGURE 6. SCH_2 and NCH_2 PMR signals of acetylthiocholine in D_2O. Recorded at 60 MHz; sweep width 250.

Note:

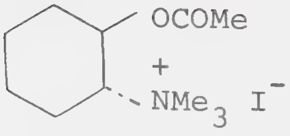
N,N-Dimethylation of cyclohexylamine with formaldehyde and formic acid produced dimethylaminocyclohexane which reacted with methyl iodide to give the corresponding methiodide salt (132). Its PMR spectrum was recorded with a view to assessing the conformational free energy ($-\Delta G^{o}_{x}$) of the trimethylammonium group by comparison with PMR data upon the cis and trans t-butyl analogs (133) (Eliel et al., 1963; Eliel, 1960). The conformational free energy value could be applied to estimate the interaction between the acetoxy and trimethylammonium group in Ach and (±)-trans- and cis-2-dimethylaminocyclohexyl acetate methiodide (30 and 31). Eliel's method requires accurate identification of the chemical shift of the α-methine proton; unfortunately, this resonance signal was obscured by the N-methyl singlet, thus making



132



133



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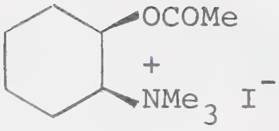
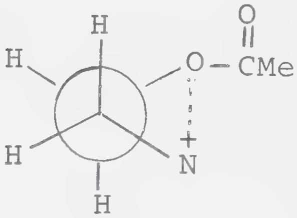


31

experimental evaluation of the $-\Delta G^{o}_{x}$ value very difficult. This approach was, therefore, given up.

ii) IR DILUTION STUDIES

Analysis of the PMR spectra of Ach and its analogs has shown that *gauche* conformers of type (134) are favored

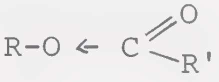


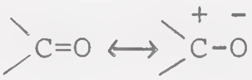
134

as the solute conformation. In these conformers a positively charged nitrogen atom is close to the acyloxy oxygen atom and an electrostatic interaction between $\overset{+}{N}$ and a lone-pair orbital of this oxygen atom might be expected to arise. This intramolecular interaction could well represent the stabilizing factor which compensates for the increased steric energy of *gauche* over

trans conformers.

Detection of an N---O interaction may be sought by a study of the carbonyl stretching frequency ($\nu_{C=O}$) in Ach and related esters. Electron withdrawal from the carbonyl group occurs via the acyloxy atom and an increase in the electronegativity of this center (135) would depress the polarization of the carbonyl group (136) with a consequent rise in the absorption frequency (Martin-Smith et al., 1967a).


135


136

Infrared data on this point is already available. Fellman and Fujita (1962) recorded the IR spectra of a series of esters in absolute ethanol (no concentration values provided) and obtained the following results:

Esters	$\nu_{C=O}$ (cm^{-1})
$MeCH_2OCOMe$	1748, 1728
$Me_2NCH_2CH_2OCOMe$	1748, 1728
$Me_3\overset{+}{N}CH_2CH_2OCOMe\ Cl^-$	1760

Thus $\nu_{C=O}$ of Ach has a significantly higher wave number than the corresponding tertiary base or ethyl acetate, consistent with the operation of an $\overset{+}{N}$---O interaction as in (134).

In the Ach analogs (137) (Fellman and Fujita, 1963), in which the N-O distance is greater that of

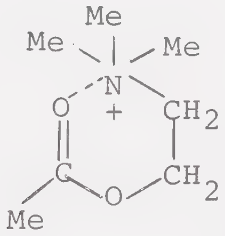
$$Me_3\overset{+}{N}(CH_2)_nOCOMe\ I^-$$

137

n=3	$\nu_{C=O}$	1752, 1732 cm^{-1}
n=4	$\nu_{C=O}$	1748, 1728 cm^{-1}

Ach, $\nu_{C=O}$ frequencies corresponded closely with those of ethyl acetate.

Fellman and Fujita (1962) originally interpreted their IR results in support of a cyclic Ach conformation (138) (this arrangement should results in a decreased



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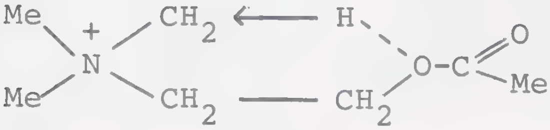
$\nu_{C=O}$ frequency) but later (1963) withdrew this hypothesis and attributed the increase $\nu_{C=O}$ values to the inductive influence of the quaternary nitrogen, acting through the choline carbon chain. This explanation has been challenged by Canepa and Mooney (1965). Canepa (1965) proposed an electrostatic interaction between $\overset{+}{N}$ and the

acyloxy oxygen atom on the basis of X-ray studies.

In 1966, Fellman and Fujita reported the possibility of a conformational interaction between the unshared electron pair on the acyloxy oxygen atom and a proton from one of the methyl groups on the quaternary nitrogen, namely $\overset{+}{\mathrm{N}}$CH---O (139) (their PMR data failed to display non-equivalence of the $\overset{+}{\mathrm{N}}\mathrm{Me}_3$ resonance signal).



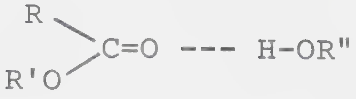
139

This postulate of the intramolecular $\overset{+}{\mathrm{N}}$CH---O interaction was reviewed by Martin-Smith and his colleagues (1967a and b) who were unable, however, to obtain conclusive evidence in support of the conformation (139) (the shifts in NC-H stretching frequencies could not be attributed to $\overset{+}{\mathrm{N}}$CH---O interaction; no PMR data were obtained to confirm this interaction). The possibility of formation of CH---O hydrogen bonds has been discussed in detail by Donohue (1968) who considered their existence to be highly improbable.

The reported IR data has two limitations:

1) its interpretation is complicated by solvent effects, the $\nu_{C=O}$ wave number of Ach and other esters will be reduced, for example, in hydroxylic solvents by

hydrogen bonding of the type (140).



140

2) there is no evidence that the $\nu_{C=O}$ wave number reduction seen in ethyl acetate on introduction of an onium group is an intramolecular effect. Dilution studies are necessary to differentiate between inter- and intra-molecular effects and these have not been reported.

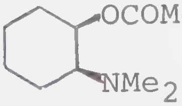
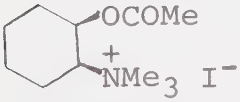
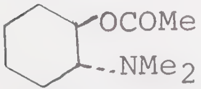
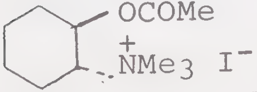
For these reasons, further IR studies of Ach and its analogs were undertaken in this work. Redistilled spectroscopic chloroform was chosen as the reference solvent since solvent effects should be negligible in this case.

Esters were examined over the concentration range 10%-0.1 or 0.05%, the lowest concentration being 0.005 mole/liter. At this dilution, intermolecular effect may be discounted (Tichý, 1965). All IR data are given in the Table 4 and only the absorption frequencies of $\nu_{C=O}$ at the initial and final concentration shown.

The comments given below may be reached on the basis of these IR results.

1. In all cases little change in the $\nu_{C=O}$ values of the salts (Table 4) occurred on dilution; this result

TABLE 4. CARBONYL STRETCHING FREQUENCIES OF ESTERS

No.	Esters	$\nu_{C=O}$ $(cm^{-1})^a$		
		10%	0.005 mole/l[b]	Others
1	$Me_3\overset{+}{N}(CH_2)_2OCOMe\ Cl^-$	1750	1755	1757[c],1740[d]
2	$Me_2N(CH_2)_2OCOMe$	1732	1732	
3	$MeCH_2OCOMe$	1735	1735	1745,1725[c]
4	$Me_2N(CH_2)_2OCOMe\cdot HCl$	1752	1757	
5	$Me_3\overset{+}{N}CH_2CH(Me)OCOMe\ Cl^-$	1745	1746	1735[d]
6	$Me_2NCH_2CH(Me)OCOMe$	1732	1732	
7	$\begin{matrix}Me\\ \underline{t}\text{-}Bu\end{matrix}\!>\!N(CH_2)_2OCOMe$	1745	1745	
8	$\begin{matrix}Me\\ \underline{t}\text{-}Bu\end{matrix}\!>\!N(CH_2)_2OCOMe\cdot HCl$	1755	1757	
9	$\begin{matrix}Me_2\\ \underline{t}\text{-}Bu\end{matrix}\!>\!\overset{+}{N}(CH_2)_2OCOMe\ I^-$	1749	1753	1742,1732[d]
10	$CH{=}CHCH_2\overset{+}{N}(CH_2)_2OCOMe\ Br^-$	1750	1755	1750[d]
11	$PhCH_2\overset{+}{N}(CH_2)_2OCOMe\ Br^-$	1750	1757	1750[d]
12	$Me_2CH\overset{+}{N}(CH_2)_2OCOMe\ Br^-$	1750	1750	1750[d]
13	$Me_3C(CH_2)_2OCOMe$	1732	1732	
14	$Me_3\overset{+}{N}(CH_2)_2SCOMe\ Cl^-$	1695	1695	
15	 (cis)	1730	1730	
16	 (cis)	1745	1750	
17	 (trans)	1730	1730	
18	 (trans)	1742	1742	

continued

TABLE 4. continued

[a] These IR spectra were recorded with a Beckman Infrared Spectophotometer Model 10. The spectral measurements in the region of carbonyl stretching frequency were calibrated with polystyrene and the error is within ±2 cm^{-1}. A KBr cell of variable path length was used.

[b] Redistilled spectroscopic chloroform was used as solvent.

[c] 10% absolute ethanol solution was used as solvent.

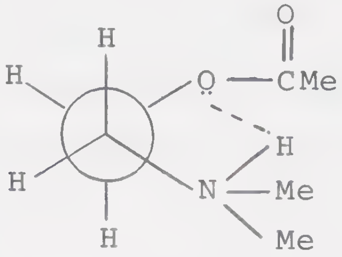
[d] Samples were examined as Nujol mulls

shows that intermolecular interactions do not significantly influence the carbonyl stretching frequency of these esters.

2. The $\nu_{C=O}$ value of Ach in chloroform (Table 4, No. 1) has a distinctly higher wave number than that of the corresponding tertiary amine (17) (Table 4, No. 2); $\nu_{C=O}$ of the latter corresponds closely with that of ethyl acetate (Table 4, No. 3) and is markedly lower than that of the amine hydrochloride (Table 4, No. 4), $\nu_{C=O}$ of this salt being about the same as that of Ach. The same difference was seen in the case β-methocholine and its corresponding free base (24) (Table 4, No. 5 and 6). These results indicate the existence of some intramolecular effect operating in the molecule of the salts, which raises the $\nu_{C=O}$ value. The shifts in $\nu_{C=O}$ between the tertiary amine of the *t*-butyl analog (Table 4, No. 7) and its hydrochloride and its methiodide (Table 3, No. 8 and 9) are, however, not large; $\nu_{C=O}$ values of the latter two are close to that of Ach, whereas that of the free base is abnormally higher than that of ethyl acetate.

3. The $\nu_{C=O}$ values of all the Ach analogs (Table 4, No. 9, 10, 11, 12), in which one of the N-methyl groups of $\overset{+}{N}Me_3$ in the Ach molecule is replaced by the bulkier group, are similar to that of Ach. The PMR data upon these salts have provided information in support of their *gauche* conformation about the $\overset{+}{N}CCO$ fragment and

the IR data obtained give further evidence of the probable existence of interactions between the nitrogen and acyloxy oxygen atoms (134). In the hydrochloride salts (Table 4, No. 4, 8), hydrogen bonding of the type (141) may also contribute to the observed $\nu_{C=O}$ increase



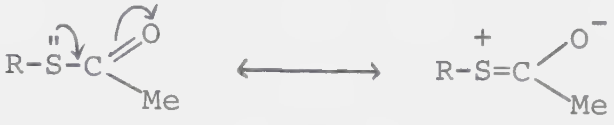
141

(if the $\overset{+}{N}H$ proton bonded to carbonyl oxygen a decreased $\nu_{C=O}$ value would result).

4. The similar $\nu_{C=O}$ values of 3,3-dimethyl-n-butyl acetate (carbocholine) (27) (Table 4, No. 13) and ethyl acetate shows that the $\nu_{C=O}$ elevation seen in Ach and related compounds is not steric in origin. In addition, results upon the free tertiary amine esters (Table 4, Nol 2, 6) and ethyl acetate establish that the basic nitrogen function has no significant influence on the ester carbonyl stretching frequency.

5. The very low $\nu_{C=O}$ value of acetylthiocholine (thioAch) (lower than that of ethyl acetate) reflects the different influence of oxygen and sulfur upon the carbonyl stretching vibration; release of a sulfur lone

pair of electrons as shown in the canonical forms (142) is responsible for lowering $\nu_{C=O}$ of thiolesters below



142

the values found for ketones (Bellamy, 1968). This wave number decrease may be attributed to the difference in electronegativity between oxygen and sulfur since the electronegativity of sulfur is substantially less than that of oxygen. The corresponding tertiary amine (143) of thioAch was not available for assessing $\overset{+}{N}$---S interactions. However, the $\nu_{C=O}$ value for thioAch falls

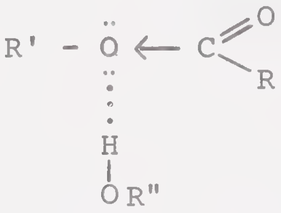
$$Me_2NCH_2CH_2SCOMe$$

143

within the range 1698-1690 cm^{-1} quoted for dialkyl thioiesters (Bellamy, 1968), and this suggests that $\overset{+}{N}$---SCOMe interactions are absent as would be the case if a trans N/S conformer were preferred.

6. Some data in $CHCl_3$ (Table 4, No. 1, 2, 3) obtained in the present work are very close to the reported data on these compounds in DMSO (1744, 1733, 1733 cm^{-1} respectively) (Fellman and Fujita, 1966); both these solvents are unlikely to associate with the carbonyl function of solute molecules. Re-examination of the values of $\nu_{C=O}$ of ethyl acetate and Ach in ethanol (Table 4, No. 3

and 1) reveals that they also are consistent with Fellman and Fujita's report (1962). In view of previous publications (Canepa and Mooney, 1965; Fellman and Fujita, 1966) and the present data, the solvent effect must be taken into account. Of striking interest is the higher wave number shift of $\nu_{C=O}$ when ethanol was used as solvent, a result which is contrary to the anticipated lower wave number shift that must follow association of ethanol's hydroxyl with the ester's carbonyl function. A possible explanation is that the ethanol interaction involves the lone pair electrons on acyloxy oxygen atom and the solvent hydroxyl group (144) as shown below; this interaction would result in an increase in the $\nu_{C=O}$ value.



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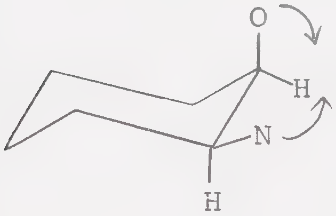
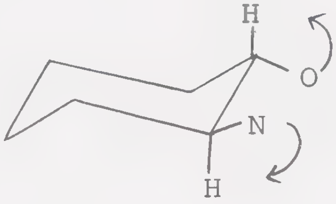
8. Carbonyl stretching frequency data upon the quaternary salts examined as Nujol mulls (Table 4, No. 1, 5, 9, 10, 11, 12) showed no consistency. In mulls the physical state varies from compound to compound.

9. The $\nu_{C=O}$ shift of the base to the quaternary salt (Table 4, No. 15 and 16) for the cis cyclic Ach analogs is significantly larger than that seen in the

trans case ($\Delta\nu_{C=O}$=20 cm^{-1} for the cis, 12 cm^{-1} for the trans at the highest dilution) (Table 4, No. 17, 18). Fellman and Fujita (1962) also reported a higher $\nu_{C=O}$ value in ethanol for the cis quaternary salt ($\nu_{C=O}$=1753 cm^{-1} for the cis, 1740 cm^{-1} for the trans) but provided no data on the corresponding free bases. These differences suggest that the nitrogen and oxygen functions may approach more closely in the cis analogs. This deduction is in accord with the interpretation of the greater reactivity of cis compared with trans esters and xanthates in pyrolytic eliminations (Eliel et al., 1965). The approach of both cis (145) and trans (146)



145



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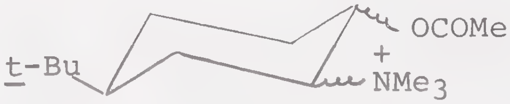
disposed groups involves ring distortion in these reactions but less non-bonded interactions result in the former case. Data on the t-butyl cyclic analogs (73)



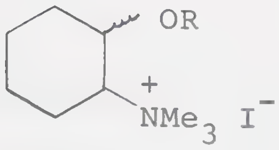
73

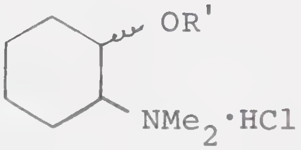
will be a valuable adjunct to these IR studies.

It is evident from these discussions that the IR results substantiate operation of intramolecular interactions of the form $\overset{+}{\mathrm{N}}\text{---O}$ (acyloxy oxygen) (134).

NOTE ON PHARMACOLOGY

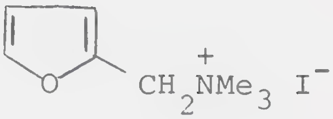
The following compounds were submitted to Professor E.R. Ariëns of the Department of Pharmacology, University of Nijmegen, for their evaluation as muscarinic and nicotinic agents.





R	Isomer		R'	Isomer	
COMe	trans	30	COMe	trans	62
COMe	cis	31	COMe	cis	64
$COCHPh_2$	trans	49	$COCHPh_2$	trans	47
$COCHPh_2$	cis	50	$COCHPh_2$	cis	48
$COC(OH)Ph_2$	trans	57	$COC(OH)Ph_2$	trans	55
$COC(OH)Ph_2$	cis	58	$COC(OH)Ph_2$	cis	56

At the time of writing this thesis only a preliminary report upon the cyclohexane analogs (30 and 31) was available (Ariëns, 1969). The *trans* isomer (30), while having a weak spasmogenic action upon the guinea pig ileum in some cases, generally acted as a weak antagonist of contractions induced by the muscarinic agent furtrethonium (147); its pA_2 value was 4.5. The *cis* isomer



(31) was practically inactive as an antagonist.

Professor Ariën's preliminary conclusion was that there appeared to be no clear-cut difference in the activity of the two isomers and that (as compared to Ach) cyclization results in a loss of intrinsic activity for the trans compound and a loss of both affinity and intrinsic activity for the cis isomer.

CHAPTER V

EXPERIMENTAL

All melting points were measured on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckmann Infrared Spectrophotometer Model 10 (solids as Nujol mulls and liquids as films unless otherwise specified). PMR spectra were determined on a Varian Associates Model A-60D spectrometer at the normal operating temperature, and the chemical shifts are recorded in Hz from tetramethylsilane (TMS) unless otherwise specified. Elemental analyses were carried out by Drs. G. Weiler and F.B., Strauss, Microanalytical Laboratory, Oxford, England, and by the microanalytical laboratories of the Department of Chemistry and of the Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta.

All the commercial chemicals were used without further purification unless otherwise specified.

i) SYNTHESIS OF ACYCLIC ACETYLCHOLINE ANALOGS

(β-Acetoxyethyl)allyldimethylammonium Bromide (13)

To an acetone solution of 2-dimethylaminoethyl acetate (17) (1.3 g, 0.01 mole) was added dropwise an acetone solution of allyl bromide (1.2 g, 0.01 mole); white crystals of (13) (2.4 g, 96%) separated spontaneously and were collected. Upon recrystallization from ethanol-ether the crude crystals gave white needles, m.p. 101-103°.

Anal. Calcd. for $C_9H_{18}BrNO_2$: C, 42.86; H, 7.19.
Found: C, 42.86; H, 7.16.

Allyldimethyl(β-hydroxyethyl)ammonium Bromide (126)

A solution of 2-dimethylaminoethanol (8.9 g, 0.1 mole) in acetone was added dropwise to allyl bromide (12.1 g, 0.1 mole) in acetone; white crystals of (126) precipitated immediately and were collected (20.5 g; 98%), m.p. 63-65° from ethanol-ether.

Anal. Calcd. for $C_7H_{16}BrNO \cdot H_2O$: C, 36.85; H, 7.95.
Found: C, 36.44; H, 8.36.

Benzyldimethyl(β-hydroxyethyl)ammonium Bromide (19)

Benzyl bromide (17.1 g, 0.1 mole) was dropwise added to an acetone solution of 2-dimethylaminoethanol (8.9 g, 0.1 mole) and the white crystals which resulted collected. Yield 21 g (81%), m.p. 129-130° (Jones, 1962, reported 130-131°).

(β-Acetoxyethyl)benzyldimethylammonium Bromide (14)

a) A mixture of 2-dimethylaminoethyl acetate (2.6 g, 0.02 mole) and benzyl bromide (3.4 g, 0.02 mole) in acetone was refluxed for 3 hours. The acetone was evaporated and the residue was cooled when it crystallized as white prisms (3 g), m.p. 124-127°.

IR spectrum:

ν_{max}: 3300 cm^{-1} (OH, vs), 1750 cm^{-1} (CO, vw).

The presence of a very weak ester $\nu_{C=O}$ peak indicated that most of ester formed had been hydrolyzed to the corresponding alcohol (water being present either in the solvent and/or absorbed from the atmosphere). The $\nu_{C=O}$ peak disappeared when the crude product was recrystallized from ethanol-acetone-petroleum ether mixture. The m.p. of the purified product was 129-130° and this was not depressed by the alcohol (19). The product was thus identified as benzyldimethyl(β-hydroxyethyl)ammonium Bromide (19).

b) A mixture of the alcohol quaternary salt (19) (5.2 g, 0.02 mole) and acetic anhydride (3.06 g, 0.03 mole) was heated under reflux for 2 hours while stirring. The white crystals (4 g) which precipitated after cooling were collected and washed with acetone; they had m.p. 127-130°, mixed m.p. (with the starting alcohol) 127-129° and an IR spectrum superimposable with the starting material.

c) Procedure b) was repeated and the reflux time was prolonged to 5 hours. The precipitate (2 g) collected melted at 128-130° and the m.p. was not depressed when mixed with the starting alcohol; this precipitate was therefore the unreacted starting alcohol. Anhydrous ether was added to the filtrate (mother liquid of the reaction mixture after removal of the above precipitate) and white crystals (2 g) melting at 124-126° was isolated. Its mixed m.ps. with the starting alcohol and with the product isolated in the d) (see later) were 110-124° and 124-126° respectively. Its IR spectrum did not display ν_{OH} peak but had a very strong $\nu_{C=O}$ band at 1750 cm^{-1} and was superimposable with the product of d).

d) A mixture of the compound (19) (5.2 g, 0.02 mole), acetic anhydride (3.06 g, 0.03 mole) and pyridine (5 ml) was stirred for 10 hours at room temperature. Removal of pyridine, excess acetic anhydride and acetic acid formed in the course of reaction under diminished pressure yielded white crystals of the title compound (5.5 g, 91.5%), m.p. 124-127°, mixed m.p. with the starting alcohol 110-124°. The crude white crystals crystallized as white rosettes from ethanol-ether and melted at 125.5-126.5°.

Anal. Calcd. for $C_{13}H_{20}BrNO_2$: C, 51.65; H, 6.68.

Found: C, 51.74; H, 6.82.

Dimethyl(β-hydroxyethyl)isopropylammonium Bromide (20)

a) An acetone solution of 2-dimethylaminoethanol (8.9 g, 0.1 mole) and isopropyl bromide (12.3 g, 0.1 mole) was refluxed for 4 hours while stirring. Evaporation of acetone gave white crystals of (20) (10 g, 47%), m.p. 275-276° with decomposition from ethanol-ether (Robinson, 1951, reported 274°).

b) A mixture of 2-dimethylaminoethanol (17.8 g, 0.2 mole) and isopropyl bromide (24.6 g, 0.2 mole) in acetonitrile was refluxed and stirred for 6 hours; white crystals separated during the reflux period. Anhydrous ether was added to the reaction mixture to bring about maximum precipitation, and the crystals (35 g, 83%), m.p. 274-276°, were collected.

(β-Acetoxyethyl)dimethylisopropylammonium Bromide (15)

a) An acetone solution of 2-dimethylaminoethyl acetate (1.3 g, 0.01 mole) and isopropyl bromide (1.2 g, 0.01) was warmed for 5 minutes, and a semisolid was obtained. Removal of the solvent afforded residue (2.2 g). Several attempts to obtain a crystalline product from ethanol-ether, methanol-ether or ethanol-acetone-ether were fruitless.

b) An acetone mixture of 2-dimethylaminoethyl acetate (2.6 g, 0.02 mole) and isopropyl bromide (2.4 g,

0.02 mole) was heated under reflux for 2 hours; crystals separated out on the wall of the reaction flask when the reaction mixture was cooled. Ether was added slowly to the mixture until maximum precipitation resulted. White needles of the title compound (0.5 g) were collected which melted at 119-120° (see d) for analysis). When the period of reflux was prolonged to 24 hours, or the mixture allowed to stand at room temperature for 7 days the yield was not improved.

c) A mixture of 2-dimethylaminoethyl acetate (2.6 g, 0.02 mole) and isopropyl bromide (2.4 g, 0.02 mole) in acetonitrile was refluxed for 24 hours. To the refluxed mixture was added anhydrous ether and white crystals of the desired product (2 g, 40%) were collected, m.p. 120-122° from an ethanol-acetone-ether mixture.

d) A mixture of (20) (10.6 g, 0.05 mole), acetic anhydride (10.2 g, 0.1 mole) and pyridine (20 ml) was stirred for 12 hours. Anhydrous ether was added to the reaction mixture and the solidified product of (15) was collected and washed with ether. Recrystallization of the solid from ethanol-acetone-ether gave white prisms of the ester (15) (11.5 g, 91%), m.p. 122-124°.

Anal. Calcd. for $C_9H_{20}BrNO_2$: C, 42.53; H, 7.93.
Found: C, 42.56; H, 8.11.

2-(N-*t*-butyl-N-methylamino)ethanol (22) Hydrochloride

A mixture of 2-*t*-Butylaminoethanol (11.7 g, 0.1 mole), 40% (w/v) formaldehyde (11.2 ml, 0.15 mole) and 88% formic

acid (7.8 g, 0.15 mole) was refluxed for 12 hours and then acidified with conc. hydrochloric acid. The solution was evaporated to dryness, the residue treated with conc. aqueous sodium hydroxide and then extracted with ether several times. Removal of ether from the dried (Na_2SO_4) ethereal extract and distillation of the residue gave the N-methylated product (22) (11 g, 85%), a colorless liquid, b.p. 68-70°/17 mm. Treatment of the free base (22) (1.3 g, 0.01 mole) with HCl-ethanol until the solution was acidic to litmus paper and addition of anhydrous ether to the acidic solution yielded the hydrochloride salt (16 g, 96%) as white needles, m.p. 133-134° from ethanol-ether.

Anal. Calcd. for $C_7H_{18}ClNO$: C, 50.14; H, 10.81.
Found: C, 50.22; H, 10.78.

t-Butyldimethyl(β-hydroxyethyl)ammonium Iodide (21)

a) A mixture of the tertiary base (22) (2 g, 0.015 mole) and methyl iodide (5 g, 0.035 mole) in methanol was heated to boiling for 2 hours. Anhydrous ether was added to this solution until it became turbid and it was then cooled. The crystals which formed were collected and recrystallized from methanol-ether. The yield of 21 was

4 g (99%), m.p. 200-202°.

Anal. Calcd. for $C_8H_{20}INO$: C, 35.18; H, 7.37.

Found: C, 35.32; H, 7.19.

b) To a solution of 2-t-butylaminoethanol (11.7 g, 0.1 mole) in anhydrous methanol was added methyl iodide (50 g) and the solution refluxed. After 1 hour's reflux freshly prepared sodium methoxide (6g) in anhydrous methanol (20 ml), was added and reflux period continued for another 3 hours. Methyl iodide (20 g) and sodium methoxide (2 g) in methanol (5 ml) were added to the refluxed solution. This addition of methyl iodide and sodium methoxide was repeated twice over the period of 24 hours.

The solution was filtered, white crystals (21) (17 g), m.p. 200-205°, being obtained. The filtrate was evaporated to dryness under reduced pressure and residue was recrystallized from ethanol, thus affording another crop (8 g) of the title compound. Total yield, 25 g (93%).

(β-Acetoxyethyl)-t-butyldimethylammonium Iodide (16)

a) A mixture of 2-dimethylaminoethyl acetate (3.9 g, 0.03 mole) and t-butyl bromide in acetonitrile was heated under reflux for 5 or 80 hours. The solvent was evaporated under reduced pressure and the residue kept in a vacuum desiccator when white, long needles

(6.2 g) were produced. Recrystallization of the needles from acetone-ethanol-ether gave crystals, m.p. 87-90°, which was not depressed when mixed with hydrobromide of 2-dimethylaminoethyl acetate with hydrogen bromide (see later).

IR spectrum:

ν_{max}: 2655 and 2475 cm^{-1} ($\nu_{\overset{+}{N}H}$), 1750 cm^{-1} ($\nu_{C=O}$)

Anal. Calcd. for $C_{10}H_{22}BrNO_2$: C, 33.75; H, 6.65.

Found: C, 33.80; H, 6.53.

The reported m.p. for hydrobromide of 2-dimethylaminoethyl acetate is 84° (Tammelin, 1957). All these data show that the product is the hydrobromide of 2-dimethylaminoethyl acetate rather than the expected quaternary ester (16).

b) An acetonitrile solution of 2-dimethylaminoethyl acetate (1.3 g, 0.01 mole) and *t*-butyl bromide (1.37 g, 0.01 mole) was stirred at room temperature for 7 days and anhydrous ether was then added to the product. White crystals (1.8 g), m.p. 86-87°, were obtained and identified as the hydrobromide of 2-dimethylaminoethyl acetate.

c) A mixture of (21) (8.2 g, 0.03 mole), acetic anhydride (5.1 g, 0.05 mole) and pyridine (30 ml) was stirred for 16 hours at room temperature. The product, processed in the same way as described in the case of the benzyl analog (14), yielded the quaternary ester

(16) (9.29 g, 97%), m.p. 173-174° with decomposition from methanol-ether.

Anal. Calcd. for $C_{10}H_{22}INO_2$: C, 38.10; H, 7.04.

Found: C, 38.07; H, 7.08.

2-Dimethylaminoethyl Acetate Hydrohalides

The hydrobromide salt was prepared by passing hydrogen bromide through an ethereal solution of 2-dimethylaminoethyl acetate (1.3 g). Yield, 2.0 g (95%), m.p. 86-87° from an acetone-alcohol-ether mixture (Tammelin, 1957, reported 84°).

The corresponding hydrochloride melted at 126-128° from alcohol-ether.

Anal. Calcd. for $C_6H_{14}ClNO_2$: C, 42.98; H, 8.41.

Found: C, 42.74; H, 8.42.

2-(N-*t*-Butyl-N-methylamino)ethyl Acetate Hydrochloride (23)

2-(N-*t*-Butyl-N-methylamino)ethanol (22) hydrochloride (3.34 g, 0.02 mole) was heated under reflux with acetic anhydride (3 g, 0.03 mole) for 24 hours. Anhydrous ether was added to the refluxed solution to bring about crystallization of the title compound. The crystals (3.5 g, 83.5%) were collected and recrystallized from ethanol-ether, m.p. 138-139°.

Anal. Calcd. for $C_9H_{20}ClNO_2$: C, 51.58; H, 9.55.

Found: C, 51.82; H, 9.80.

The free base liberated from the salt (23), was used for IR dilution studies without further purification.

2-Dimethylamino-1-methylethyl Acetate (24)

A solution of 2-dimethylamino-1-methylethyl alcohol (10.3 g, 0.1 mole) in dry toluene was added dropwise to a solution of acetyl chloride (15.7 g, 0.2 mole) in dry toluene. The resulting crystals were collected, treated with a slight excess of dilute ammonia and extracted with ether. The ether of the dried (Na_2SO_4) extract was evaporated and the residue distilled under water pressure to give the title compound (10 g, 69%), b.p. 47°/14 mm (Tammelin, 1957, reported 53°/13 mm).

Hydrobromide (25): m.p. 113-115° from ethanol-ether (Tammelin, 1957, reported 121°).

2-Aminoethyl Acetate Hydrochloride (26)

a) 2-Aminoethanol (10 g, 0.16 mole) was cooled to 0°C and glacial acetic acid (11 g) was added dropwise, the temperature during the addition being kept below 5°C. The mixture which became solid after the addition, was stirred with anhydrous ether and the ethereal suspension (at -10°C) then treated with anhydrous hydrogen chloride until it was saturated. The product was allowed to stand at room temperature overnight. Excess of hydrogen chloride was removed in a current of air, and the

residue collected and washed with acetone. Recrystallization of the collected crystals from ethanol-ether gave white needles (14 g), m.p. 80-82°, mixed m.p. with 2-aminoethanol hydrochloride (prepared by the previous method for making amine hydrochloride), 80-83°. This product was identified as 2-aminoethanol hydrochloride instead of its acetate (26).

b) 2-Aminoethanol hydrochloride was prepared by treating 2-aminoethanol with ethanol-HCl and melted at 81-83° (75-77°, Merck Index, 1968). A mixture of this salt (14 g, 0.14 mole) and acetyl chloride (22 g, 0.28 mole) in acetone was heated and stirred for 30 minutes. The mixture was cooled, filtered and washed with a few ml. of acetone, thus yielding the title ester (19 g, 98%), m.p. 127-129° (Crane and Rydon, 1947, reported 130°; Hansen, 1963, 132°).

3,3-Dimethyl-*n*-butyl Acetate (27)

3,3-Dimethyl-*n*-butyl alcohol (10 g, 0.1 mole), and acetic anhydride (10 g, 0.1 mole) were heated under reflux for 3 hours. The reaction mixture was washed with 10% aqueous sodium bicarbonate until evolution of carbon dioxide ceased. The oily layer was separated, washed with water and dried over anhydrous sodium sulfate. Distillation of the crude oil (13 g) gave the title ester (27) (12.8 g, 88%), b.p. 152-154° at atmospheric pressure, 47-48°/14 mm (Burgen, 1965, reported 154° at atmospheric pressure).

ii) SYNTHESIS OF SIMPLE CYCLOHEXANE ACETYLCHOLINE ANALOGS

(±)-trans-2-Benzaminocyclohexanol (38)

A mixture of cyclohexene oxide (100 g, 1.02 moles) benzylamine (109 g, 1.02 moles) and water (15 ml) was refluxed for 5 hours and then extracted with ether. The ethereal extract was dried (Na_2SO_4) and filtered, and the filtrate evaporated to dryness, thus affording 205 g of the title compound which upon recrystallization from petroleum ether melted at 71-73° (Kovar, 1958, reported 73°).

(±)-trans-2-Aminocyclohexanol (35)

A mixture of the aminoalcohol (38) (205 g, 1 mole) and 10% palladium on charcoal (20 g) in absolute alcohol was shaken with hydrogen at room temperature and pressure until the theoretical amount of hydrogen had been absorbed. The mixture was filtered and the solvent, alcohol, was taken off under reduced pressure. The residue was purified by distillation to give the title compound (35) (110 g, 96%), b.p. 111-112°/17 mm, m.p. 65° (McCasland *et al.*, 1949, reported b.p. 102-107°/9 mm, m.p. 68°). It gave a hydrochloride, m.p. 177° from ethanol-ether (McCasland *et al.*, 1949, reported 176-177°).

(±)-trans-2-Dimethylaminocyclohexanol (28)

The *trans* aminoalcohol (35) (11.5 g, 0.1 mole), 40% aqueous formaldehyde (22 ml) and 88% formic acid

(13.8 g) were refluxed for 12 hours. The mixture was then acidified with conc. hydrochloric acid and evaporated to dryness under reduced pressure. The residue, after being made alkaline with 10% aqueous sodium hydroxide and saturated with sodium chloride, was extracted with several portions of ether. The combined ether extracts were dried (Na_2SO_4), the solvent removed, and the product distilled to yield the title compound (9.3 g, 80.5%), b.p. 91-92°/17 mm (Adank and Stoll, 1959, reported 78-80°/11 mm; Taguchi et al., 1963, reported 71-75°/10 mm). It gave a hydrochloride, m.p. 186° from ethanol-ether (Adank and Stoll, 1959, reported 186-188°).

(±)-trans-2-Dimethylaminocyclohexyl Acetate Hydrochloride (62)

A toluene solution of the trans dimethylamino-alcohol (28) (4.0 g, 0.028 mole) was stirred with acetyl chloride (2.2 g, 0.028 mole) in toluene for 1 hour, when white crystals (6.2 g, 100%) of the desired ester HCl were collected. This formed white prisms upon recrystallization from ethanol-ether which melted at 187-189°. Anal. Calcd. for $C_{10}H_{20}ClNO_2$: C, 54.21; H, 9.03. Found: C, 54.38; H, 9.04.

(±)-trans-2-Dimethylaminocyclohexyl Acetate

The title compound was obtained in 90% yield by

treating the corresponding hydrochloride (62) with excess of dilute ammonia. Its boiling point was 111-112°/18 mm (Adank and Stoll, 1959, reported 105-108°/15 mm).

(±)-*trans*-2-Dimethylaminocyclohexyl Acetate Methiodide (30)

An absolute ethanolic solution of (±)-*trans*-2-dimethylaminocyclohexyl acetate (0.8 g, 0.004 mole) and methyl iodide (1.7 g, 0.012 mole) was stirred for 3 hours. To this solution was added anhydrous ether to bring about complete precipitation. The product (1.3 g, 93%) when recrystallized from ethanol-ether gave white rosettes melting at 148-149°; when recrystallized from ethanol-ether containing 2 drops of water the product melted at 145-149°. (Baldridge *et al*., 1955, reported 210-211° for monohydrate; Adank and Stoll, 1959, 134-135°; Kay and Robinson, 1969, 161-165°). The sample used for microanalysis melted at 149-151°.

Anal. Calcd. for $C_{11}H_{22}INO_2$: C, 40.38; H, 6.78.
Found: C, 40.27; H, 6.75.

(±)-*trans*-2-Dimethylaminocyclohexanol Methiodide (39)

The title compound was prepared in 95% yield similarly to that described for (30) and melted at 217-218° from methanol-ether (Adank and Stoll, 1959, reported 221-222°; Baldridge *et al*., 1955, 210-212°).

(±)-trans-2-p-Nitrobenzamidocyclohexanol (36)

A benzene solution of p-nitrobenzoyl chloride (18.5 g, 0.1 mole) was added to an aqueous solution of the trans aminoalcohol (35) (11.5 g, 0.1 mole), followed by the gradual addition of 5% aqueous sodium hydroxide (80 ml). The amide which formed in the upper layer of the reaction mixture was filtered and recrystallized from 95% alcohol to give pale yellow needles (25.6 g, 96.5%), m.p. 210-212° (Leffer and Adams, 1937, reported 210-211°).

(±)-2-p-Nitrophenyl-4,5-cis-cyclohexanoöxazoline-2 (37)

The trans-p-nitrobenzamide (36) (13.2 g, 0.05 mole) was treated at room temperature with thionyl chloride (43.6 g, 0.4 mole). After 6 hours stirring, the yellow solution was poured into dry ether at 0°. The pale yellow precipitate which formed was collected, sucked free from thionyl chloride as much as possible, and then suspended in ether and stirred. The ether was removed by filtration and the solid resuspended in water and stirred. The water treatment resulted in an exothermic reaction and most of the solid dissolved. The product was filtered free from impurities and the filtrate neutralized with conc. sodium hydroxide, giving a white precipitate, the title compound, which recrystallized from absolute alcohol as pale yellow needles melting at 118-120° (McCasland and Smith, 1950, reported 120-121°).

The residue obtained from the filtration of aqueous washings melted at 233-234° with decomposition and was identified as (±)-cis-2-aminocyclohexyl-p-nitrobenzoate hydrochloride by mixed m.p. with a known sample (40) (syntheses see below).

The yield of the oxazoline and the aminoester hydrochloride varied from batch to batch.

(±)-cis-2-Aminocyclohexyl-p-nitrobenzoate Hydrochloride (40)

a) A solution of the oxazoline (2.3 g, 0.01 mole) in 5% hydrochloric acid (20 ml) was heated until it boiled and then allowed to cool. The product crystallized in pale yellow needles (2.5 g, 87%), m.p. 231-233° with decomposition (McCasland and Smith, 1950, reported 230-232°. The m.p. was 233-234° after recrystallization from alcohol.

b) A mixture of the trans p-nitrobenzene (36) (64.5 g, 0.025 mole) and thionyl chloride (270 g, 2.27 moles) was stirred at room temperature for 6 hours. Water (400 ml) was carefully poured into the above solution. The resulting solution was filtered, thus yielding (27 g), m.p. 230-232° with decomposition. The filtrate was boiled for 10 min., followed by cooling, when yellow needles (17 g) crystallized from the solution. The mother liquid was concentrated, cooled and filtered,

another crop of product (20 g) being collected. The m.p. of the second and third crops was the same as that of the first crop. Yield, 64 g (87%).

IR spectrum:

ν_{max}: 2630 and 2540 cm^{-1} ($\overset{+}{N}H$), 1730 cm^{-1} (ester CO).

(±)-cis-2-p-Nitrobenzamidocyclohexanol (41)

A suspension of the cis aminoester hydrochloride (40) (64 g, 0.2 mole) in water (1 litre) was made basic with conc. sodium hydroxide. The voluminous white precipitate which formed was collected and recrystallized from 95% ethanol, thus giving pale yellow needles (54 g, 96%), m.p. 173-175° (McCasland and Smith, 1950, reported 173-175°).

IR spectrum:

ν_{max}: 3450 and 3295 cm^{-1} (OH), 1620 cm^{-1} (amide CO).

(±)-trans-2-Benzamidocyclohexanol (42)

To the trans aminoalcohol (35) (34.5 g, 0.3 mole) dissolved in water (200 ml) was added benzoyl chloride (70.3 g, 0.5 mole) and a solution of sodium hydroxide (20 g, 0.5 mole)-water (120 ml). After 20 minutes swirling, the amide (65 g, 99%) m.p. 162-165° (Winstein and Boschan, 1950, reported 171-172°), was obtained.

(±)-cis-2-Benzamidocyclohexanol (43)

(±)-trans-2-Benzamidocyclohexanol (60 g, 0.274 mole) was added in small portions to thionyl chloride (60 ml) (cooled by crushed ice). More thionyl chloride (20 ml) was added to bring a small amount of undissolved material into solution. The mixture was allowed to warm to room temperature and left for three hours, then the mixture was carefully poured into water (1.5 liters). The resulting solution was filtered and the filtrate was refluxed for 10 min. After refluxing, the solution was kept in a refrigerator for 24 hours and filtered, and conc. sodium hydroxide was added to basify the filtrate. The cis amide (43), which separated, melted at 180-181° (Winstein and Boschan, 1950, reported 180-182°); the yield was 54 g (90%).

IR spectrum:

ν_{max}: 3320 and 3270 cm^{-1} (OH), 1625 cm^{-1} (amide CO).

(±)-cis-2-Aminocyclohexanol (34)

a) Hydrolysis of the cis oxazoline (37) by aqueous hydrochloric acid.

A mixture of the oxazoline (37) (10 g, 0.042 mole) in 4N hydrochloric acid (75 ml) was refluxed for 4 hours, followed by cooling and filtration. The filtrate was evaporated to dryness, made alkaline with conc. sodium hydroxide and extracted with ether-chloroform (1:1).

Evaporation of the dried (Na_2SO_4) ethereal extract gave a crude product (2 g) which upon distillation afforded the aminoalcohol (34) (1 g, 23.5%), b.p. 112-114°/16 mm, m.p. 74-75° (McCasland *et al.*, 1949, reported 72-73°).

The IR spectrum of the residue obtained from the refluxed mixture had a few characteristic absorptions such as 2630 and 2540 cm^{-1}, 1730 cm^{-1} and 1695 cm^{-1} and was completely superimposable with that of a prepared mixture of the *cis* aminoester hydrochloride (40) and *p*-nitrobenzoic acid (the $\nu_{C=O}$ of *p*-nitrobenzoic acid is at 1695 cm^{-1}). The relative intensity of $\nu_{C=O}$ at 1730 cm^{-1} to that at 1695 cm^{-1} was variable from batch to batch.

The total residue when subjected to 5% ethanolic potassium hydroxide gave aminoalcohol (34) (2 g) (detailed procedure will be described in the basic hydrolysis of the *p*-Nitrobenzamide derivative 41).

b) Hydrolysis of the *cis* oxazoline (37) by aqueous hydrochloric acid in ethanol.

The procedure a) was employed, 95% ethanol (65 ml) and conc. hydrochloric acid (10 ml) was used instead of 4N aqueous hydrochloric acid, and the reflux period was prolonged to 12 hours. The title compound (34) (0.7 g) was isolated from the *cis* oxazoline (37) (10 g).

c) Hydrolysis of the aminoester hydrochloride (40) by aqueous hydrochloric acid.

The aminoester hydrochloride (40) (3 g, 0.01 mole)

when subjected to 4 or 12 hours reflux with 4N hydrochloric acid (20 ml) gave the product (34) (0.2 g, 17.5%).

d) Hydrolysis of the aminoester hydrochloride (40) by aqueous hydrochloric acid in alcohol.

A solution of the aminoester hydrochloride (12 g, 0.04 mole) in a mixture of conc. hydrochloric acid (10 ml) and 95% ethanol (10 ml) was refluxed for 16 hours and gave the title compound (34) (1 g, 21.7%).

e) Hydrolysis of the p-nitrobenzamide (41) by aqueous hydrochloric acid.

A suspension of the p-nitrobenzamide (41) (16 g, 0.6 mole) in 4N hydrochloric acid (120 ml) was refluxed for 3 hours, cooled and filtered. The filtrate was evaporated to dryness and the residue was basified with conc. sodium hydroxide and extracted with ether. Removal of the solvent from the extracts and distillation of residue gave the product (34) (1.5 g, 21.4%). The yield was not significantly improved when the reflux period was prolonged.

The IR spectrum of the residue isolated from the filtration of the reaction mixture was identical with that of a prepared mixture of the cis aminoester hydrochloride (40) and p-nitrobenzoic acid. This indicates that N → O migration happened during the reaction process and this migration was proved in the following experiments.

f) Hydrolysis of the *p*-nitrobenzamide (41) by aqueous hydrochloric acid in ethanol.

A solution of the nitrobenzamide (41) (20.5 g, 0.08 mole) in a mixture of 6N hydrochloric acid (100 ml) and 95% ethanol (50 ml) was refluxed for 10 hours. The reaction mixture was treated as previously described, the product (34) (2 g, 25.6%) being isolated.

The residue of the reaction mixture also showed an IR spectrum consistent with that of aminoester hydrochloride and *p*-nitrobenzoic acid mixture.

When the reaction was carried out for 48 hours reflux, the yield was not improved.

g) Hydrolysis of the benzamide (43) by aqueous hydrochloride acid.

A mixture of the benzamide (43) (20 g, 0.09 mole) in 4N hydrochloric acid (100 ml) was refluxed for 11 hours. The precipitate of benzoic acid, m.p. and mixed m.p. (with the authentic benzoic acid) 115-120°, was removed and the filtrate concentrated and cooled when white crystals (10 g) separated, m.p. 214-216°. Upon recrystallization from ethanol-ether the m.p. was raised to 228-229° which was the same as the reported data (228°) for *cis*-2-aminocyclohexylbenzoate hydrochloride obtained by heating the benzamide (43) in a sealed tube (Fodor and Kiss, 1950). Its IR spectrum showed two characteristic bands for the assigned compound, 2700-2450 cm^{-1} $(\nu_{\overset{+}{\mathrm{N}}\mathrm{H}})$

and 1725 cm^{-1} (ester $\nu_{C=O}$), and no absorptions for ν_{OH} and $\nu_{C=O}$ of amide. The mother liquid was evaporated to dryness and its IR spectrum had, in addition to characteristic peaks for cis-2-aminocyclohexylbenzoate hydrochloride, a ν_{OH} peak at 3390 cm^{-1} which was identical with that of cis-2-aminocyclohexanol hydrochloride and different from that of the starting material (3330 and 3280 cm^{-1} for ν_{OH}).

h) Basic hydrolysis of the p-nitrobenzamide (40)

The p-nitrobenzamide (13.1 g, 0.05 mole) was dissolved in 5% ethanolic potassium hydroxide (300 ml), and the solution was refluxed for 36 hours. The cooled reaction mixture was then filtered and the solvent was evaporated under diminished pressure. The residue was extracted with ether, and the ethereal extract was washed with saturated aqueous sodium chloride, dried (Na_2SO_4) and evaporated to dryness, thus giving the cis aminoalcohol (34) (5.2 g, 90%), m.p. 74-75°.

i) Basic hydrolysis of the benzamide (43)

The previous procedure was followed and the benzamide (10 g, 0.05 mole) produced the title compound (34) (5 g, 95%), m.p. 74-75°.

j) Basic hydrolysis of the p-nitrobenzamide (41) in the presence of aqueous potassium hydroxide.

A mixture of the p-nitrobenzamide (41) (13.1 g, 0.05 mole) and 10% aqueous potassium hydroxide (40 ml)

was refluxed for 24 hours while stirring. The mixture was filtered, white crystals (10 g), m.p. of which was not depressed when mixed with the starting material, being collected. The filtrate was evaporated to dryness, and the residue was extracted with ether. The ethereal extract after being dried (Na_2SO_4) gave the title compound (0.5 g), m.p. 73-74°.

k) Basic hydrolysis of the aminoester hydrochloride (40).

The aminoester hydrochloride (40) (3 g, 0.01 mole) was produced as described in procedure h) and converted to the aminoalcohol (34) (1 g, 87%); m.p. 72-73°.

(±)-*cis*-2-Aminocyclohexanol Hydrochloride

The hydrochloride was obtained in quantitative yield by treating the base (34) with ethanol-HCl; it melted at 183-184° (McCasland *et al*., 1949, reported 189-190°).

(±)-*cis*-Dimethylaminocyclohexanol (29)

The *cis* aminoalcohol (34) (8.5 g, 0.07 mole) was N,N-dimethylated as previously described (see *trans* analog) to give the tertiary amine (29) (9.5 g, 80%), b.p. 102-104°/17 mm, m.p. 42-44° (Adank and Stoll, 1959, reported b.p. 95-97°/15 mm, m.p. 40-42°). It gave a hydrochloride, m.p. 183-184° from ethanol-ether (Adank and Stoll, 1959, reported 182-183°).

(±)-*cis*-2-Dimethylaminocyclohexyl Acetate Hydrochloride (64)

A toluene solution of the *cis* dimethylaminoalcohol (29) (2.0 g, 0.014 mole) and acetyl chloride (1.1 g, 0.014 mole) was stirred for 1 hour, when the hydrochloride (64) (3.0 g, 99%) was collected. Recrystallization of the salt from ethanol-ether afforded white prisms, m.p. 137-138°.

Anal. Calcd. for $C_{10}H_{20}ClNO_2$: C, 54.21; H, 9.03.
Found: C, 54.50; H, 8.98.

(±)-*cis*-2-Dimethylaminocyclohexyl Acetate

The acetate was obtained in 92% yield by treating the corresponding hydrochloride (64) with dilute ammonia, b.p. 110-112°/16 mm, (Adank and Stoll, 1959, reported 100-102°/11 mm).

(±)-*cis*-2-Dimethylaminocyclohexyl Acetate Methiodide (31)

The methiodide was prepared as before in 91% yield, m.p. 182-184° from methanol-ether (Baldridge *et al*., 1955, reported 182-183°; Adank and Stoll, 1959, 185-186°).

(±)-*cis*-2-Dimethylaminocyclohexanol Methiodide

This compound was prepared in 90% yield by the usual method used before, m.p. 244-246° from ethanol-

ether (Baldridge *et al.*, 1955, reported m.p. 244-245°; Adank and Stoll, 1959, 251-252°).

(±)-*cis*-2-Benzylaminocyclohexanol (*38*)

Benzyl chloride (0.45 g, 0.003 mole) in ether was added dropwise to a refluxed and stirred mixture of the *cis* aminoalcohol (*34*) (0.33 g, 0.003 mole) and anhydrous K_2CO_3 in ether. After the addition of benzyl chloride, the mixture was refluxed for another 6 hours. The precipitate was removed and the filtrate was evaporated to dryness. The residue was acidified with dilute hydrochloric acid, and extracted with ether. The aqueous portion was then made basic with conc. sodium hydroxide and extracted with ether. The combined extracts obtained from the alkaline solution were dried (Na_2SO_4) and the ether was removed, thus giving the title compound (0.2 g, 30%), m.p. 62-63° (Kover, 1958, reported 67°). It gave a hydrochloride, m.p. 245-246° (Kover, 1958, reported 248-250°).

Diphenylacetyl Chloride (*46*)

A mixture of diphenylacetic acid (20 g, 0.094 mole) and thionyl chloride (23.8 g, 0.2 mole) was refluxed for 10 hours, and the excess of thionyl chloride was taken off under reduced pressure, thus affording white crystals of (*46*) (20 g, 92%), melting at 54-56°. Recrystallization

from ligroine gave white prisms, m.p. 56-57° (56-57°, Merck Index, 1968).

(±)-trans-2-Dimethylaminocyclohexyl Diphenylacetate Hydrochloride (47)

A benzene solution of (±)-trans-2-dimethylaminocyclohexanol (28) (4.3 g, 0.03 mole) and diphenylacetyl chloride (6.9 g, 0.03 mole) was stirred for 30 minutes at room temperature, when a white precipitate separated at the bottom of the solution. This material was collected and recrystallized from ethanol-ether to give the title compound (11 g, 98%), m.p. 203-204°.

IR spectrum:

ν_{max}: 3525 and 3455 cm^{-1} (overtone of CO, weak to medium), 2580-2310 ($\overset{+}{N}H$), 1745 cm^{-1} (CO).

Anal. Calcd. for $C_{22}H_{28}ClNO_2$: C, 69.81; H, 7.55.

Found: C, 70.09; H, 7.57.

(±)-trans-2-Dimethylaminocyclohexyl Diphenylacetate Methiodide (49)

The ester hydrochloride (47) (7 g) was neutralized with dilute ammonia and extracted with ether. The extract was dried (Na_2SO_4), the solvent evaporated to leave the crude free base ester (6.5 g), (±)-trans-dimethylaminocyclohexyl diphenylacetate.

The basic ester (3.3 g, 0.01 mole) was mixed with methyl iodide (2.8 g, 0.02 mole) in ethanol, and the

mixture stirred overnight at room temperature. Dry ether was then added to the reaction mixture until precipitation was complete. Upon recrystallization from ethanol-ethyl acetate-ether, the collected precipitate gave the title compound (4.2 g, 90%) in white rosettes, m.p. 176-178°.

Anal. Calcd. for $C_{23}H_{30}INO_2$: C, 57.61; H, 6.30.

Found: C, 57.57; H, 6.66.

(±)-*cis*-2-Dimethylaminocyclohexyl Diphenylacetate Hydrochloride (48)

This was obtained in high yield by the method described for the corresponding *trans* isomer. Its m.p. was 175-176° from ethanol-ether.

IR spectrum:

ν_{max}: 3500 and 3420 cm^{-1} (overtone of CO, w), 2600-2400 cm^{-1} ($\overset{+}{N}H$), 1740 cm^{-1} (CO).

Anal. Calcd. for $C_{23}H_{30}INO_2$: C, 69.81; H, 7.55.

Found: C, 69.88; H, 7.88.

(±)-*cis*-2-Dimethylaminocyclohexyl Diphenylacetate Methiodide (50)

The procedure employed to make the *trans* isomer (49) was used to prepare the title compound. The crude (±)-*cis*-2-dimethylaminocyclohexyl diphenylacetate (3.3 g) yielded the title compound (4.3 g, 92%) as white prisms,

m.p. 164-165° from ethanol-ethyl acetate-ether.
Anal. Calcd. for $C_{23}H_{30}INO_2$: C, 57.61; H, 6.30.
Found: C, 57.41; H, 6.45.

(±)-trans-2-Dimethylaminocyclohexyl Benzilate (51)

The trans-esterification procedure of Cannon (1960) was used. Methyl benzilate (commercially available) (4.3 g, 0.03 mole) was placed together with (±)-trans-2-dimethylaminocyclohexanol (28) (7.3 g, 0.03 mole) in a 1-liter three necked flask, equipped with a Dean-Stark moisture determination apparatus topped with a condenser and a calcium chloride tube. Dry n-heptane (600 ml) and solid sodium methoxide (0.1 g) were added to the flask, and the mixture was heated and stirred. Additional sodium methoxide (0.1 g) was added after an hour reflux period. From time to time, the contents in the Dean-Stark apparatus were drained and discarded, and fresh portions of n-heptane were added to the flask to maintain the original volume. After 12 hours reflux, further sodium methoxide (0.1 g) was added. Reflux was continued for a total of 20 hours; the reaction mixture was then cooled and washed several times with water until the washings were neutral to litmus paper. The solvent was removed from the organic solution under reduced pressure in a water bath; the residue was dissolved in ether and this solution dried (Na_2SO_4) filtered, and

evaporated, thus yielding the title compound (10 g, 94%) as an oil which was used for the further reactions without purification.

(±)-trans-2-Dimethylaminocyclohexyl Benzilate Hydrochloride (55)

Treatment of the crude benzilate (51) (3.3 g, 0.01 mole) with alcohol solution saturated with hydrogen chloride gave the title compound (3.5 g, 95%) as a solid. On recrystallization from ethanol-95% ethanol it gave white prisms melting at 232-233° with decomposition (Adank and Stoll, 1959, reported 227-229° from ethanol; King and Holmes, 1947, reported 230-231° from aqueous ethanol).

Anal. Calcd. for $C_{22}H_{28}ClNO_3$: C, 67.78; H, 7.24.
Found: C, 67.99; H, 7.29.

(±)-trans-2-Dimethylaminocyclohexyl Benzilate Methiodide (57)

The crude benzilate (51) (3.5 g, 0.01 mole) was stirred with methyl iodide (5.2 g, 0.03 mole) in ethanol for 2 hours at room temperature; anhydrous ether was then added to precipitate the desired salt (57) (4.6 g, 94%). The product on recrystallization from methanol-ethanol formed white prisms and melted at 153-155°. (King and Holmes, 1947, reported 145-146° for the monohydrate).

Anal. Calcd. for $C_{23}H_{30}INO_3 \cdot H_2O$: C, 53.81; H, 6.29. Found: C, 54.08; H, 6.47.

(±)-cis-2-Dimethylaminocyclohexyl Benzilate (52)

The title compound was obtained in 93% yield from (±)-cis-2-dimethylaminocyclohexanol (29) in the same manner as that described for making the corresponding trans isomer (51).

(±)-cis-2-Dimethylaminocyclohexyl Benzilate Hydrochloride (56)

Treatment of the cis crude benzilate (52) with ethanol-HCl gave the title compound in 98% yield, m.p. 264-265° from a mixture of chloroform-ethanol-ether (Adank and Stoll, 1959, reported 265-267°).

(±)-cis-2-Dimethylaminocyclohexyl Benzilate Methiodide (58)

Treatment of the cis crude benzilate (3.5 g, 0.01 mole) with methyl iodide (5.2 g 0.03 mole) in ethanol gave the title compound (4.5 g, 92%), m.p. 238-240° from ether-chloroform (Adank and Stoll, 1959, reported 252-253° from abs. ethanol).

iii) SYNTHESIS OF 4-t-BUTYL-2-AMINOCYCLOHEXANOLS AND THEIR DERIVATIVES

4-t-Butylcyclohexene (78)

Commercial 4-t-butylcyclohexanol (60 g, 0.4 mole) was dissolved in pyridine (100 ml) and the solution treated with methanesulfonyl chloride (68.8 g, 0.6 mole) in portions under cooling by a dry ice-acetone mixture. The mixture was allowed to stand at room temperature for 24 hours, carefully treated with water to decompose the excess of the chloride and then poured into water (600 ml). The crystals were collected, the dried product (75 g) suspended in collidine (50 ml), and the suspension heated to boiling for 12 hours under intensive stirring. The solution was cooled and poured onto a mixture of ice and hydrochloric acid and the product extracted with ether. The combined extracts were dried (Na_2SO_4), the solvent taken off and the residue distilled under reduced pressure, yielding the title compound (38 g, 70%) b.p. 56-60°/15 mm, n_D^{24} 1.4593 (Sicher *et al.*, 1961, reported b.p. 54-55°/10 mm, n_D^{20} 1.4587).

PMR characteristics (CCl_4):

52 Hz (t-Bu, singlet), 336 Hz (vinylic protons, broad doublet).

Dehydration Product (93) of 4-t-Butylcyclohexanol by Phosphoric Acid

A mixture of 4-t-butylcyclohexanol (65 g, 0.42 mole) and 85% orthophosphoric acid (18 g) in a flask, to which a fractionating column was attached, was heated at 90° for 30 minutes and then the temperature raised to 160°. The water formed during the reaction together with the desired olefins, distilled below 165°. The water in the distillate was separated from the oily layer, the latter being saturated with sodium chloride and decanted, thus affording the crude olefin product (55 g, 95%), b.p. 63°/16 mm.

PMR characteristics (CCl_4)

52 Hz (t-Bu, strong singlet), 61 Hz (t-Bu, weak singlet; intensity of this singlet varied from batch to batch), 324 Hz (vinylic protons, broad signal), 336 Hz (vinylic protons, broad doublet).

This dehydration product was probably a mixture of 2,3, and 4-t-butylcyclohexene.

Studies of Isomerizarion of Olefin under Acid Conditions

a) A mixture of 4-t-butylcyclohexanol (4 g) and 85% orthophosphoric acid was heated for 1.5 hours and extracted with ether. The combined extracts were dried (Na_2SO_4) and the ether evaporated. The residue was used for PMR study. The PMR spectrum of this residue was the

same as that of (93) except the intensity of the singlet at 61 Hz was relatively greater.

The intensity ratio of the peak at 52 Hz to that at 61 Hz was 4.5:1 (calculated on the basis of the integral of each singlet).

b) The procedure of a) was applied but the reflux time was 4 hours. The intensity ratio was 2.64:1.

c) The procedure of a) was repeated and the time for heating was 17 hours. The intensity ratio was 1.48:1.

Perbenzoic Acid

50% hydrogen peroxide (31 g, 0.45 mole) was added dropwise to a slurry of benzoic acid (36.6 g, 0.3 mole) in methanesulfonic acid (86.5 g, 0.9 mole) with efficient agitation and the temperature maintained at 20-30° by means of an ice-water bath. After the addition was complete the mixture was still in a slurry form rather than a clear solution. The mixture was stirred for another 4 hours and then cooled below 15°. Chopped ice (50 g) and ice-cold saturated ammonium sulfate solution were cautiously added in sequence while the temperature was maintained below 15°.

The reaction mixture was extracted with four 50 ml. portions of benzene. The combined benzene extracts were washed three times with cold saturated $(NH_4)_2SO_4$ and filtered. Iodometric titration with sodium thiosulfate of an aliquot of the benzene solution indicated that the

yield of perbenzoic acid was 35% (Silbert *et al.*, 1963).

4-*t*-Butylcyclohexene Oxide (79)

To an ice-cold, mechanically stirred mixture of 4-*t*-butylcyclohexene (78) (13.8 g, 0.1 mole) and anhydrous sodium carbonate (32 g, 0.3 mole) in methylene chloride (200 ml) was added dropwise commercial 40% peracetic acid (22 g, 0.11 mole) which had been treated with a small amount of sodium acetate. The mixture was stirred at room temperature until the methylene chloride solution gave a negative test with moist starch-iodide paper; 40% peracetic acid (3 g) was added to the solution again and stirred for another 24 hours until the solution maintained a positive test with moist starch-iodide paper. The solvent was removed by distillation at atmospheric pressure and the residue distilled through a fractionating column to give the epoxide (79) as a colorless liquid (12.5 g, 81%), b.p. 80-94°/16 mm (Sicher *et al.*, 1961, reported 78-80°/9 mm). Use of perbenzoic acid led to a similar product.

PMR characteristics (CCl_4):

50 Hz (*t*-Bu, singlet), 177 Hz (epoxide ring protons, broad doublet); no vinylic proton signal.

A fraction of a colorless liquid, b.p. 68-76°/16 mm showed a mixture of the starting olefin and the desired epoxide.

PMR characteristics (CCl_4):

50 Hz (t-Bu of the epoxide), 52 Hz (t-Bu of the olefin), 177 Hz (epoxide ring protons), 336 Hz (vinylic protons).

Epoxidation Product (94) of the Olefin Mixture (93)

The procedure used to prepare 4-t-butylcyclohexene oxide (79) was repeated. The olefin mixture (93) (53.5 g, 0.39 mole) gave a colorless liquid (50 g, 83%), b.p. 76-85°/16 mm. which might be composed of 2, 3 and 4-t-butylcyclohexene oxide.

PMR characteristics (CCl_4):

50 Hz (t-Bu, singlet), 53 Hz (t-Bu singlet), 58 Hz (t-Bu, singlet), 177 Hz (epoxide ring protons, broad).

PMR characteristics ($CDCl_3$):

50 Hz (t-Bu), 55 Hz (t-Bu), 58 Hz (t-Bu), 138 Hz (epoxide ring protons).

A colorless liquid (5 g), b.p. 68-76°/16 mm was also obtained and was a mixture of the starting olefins and epoxides.

PMR characteristics (CCl_4):

50, 52, 58 and 61 Hz (t-Bu), 177 Hz (epoxide ring protons), 324 and 336 Hz (vinylic protons).

Ring Opening Mixture (95) Derived From 4-t-Butylcyclohexene Oxide (79) and Benzylamine

A mixture of 4-t-butylcyclohexene oxide (12 g, 0.078

mole), benzylamine (8.4 g, 0.078 mole) and water (10 ml) was heated to boiling for 24 hours. The mixture was extracted with ether and the solvent evaporated under diminished pressure. The residue was distilled (using a water pump) and a fraction (4 g), b.p. 60-80°/16 mm, collected. This was a mixture of the epoxide and benzylamine.

PMR characteristics ($CDCl_3$)

Epoxide: 50 Hz (t-Bu), 138 Hz (ring proton); benzylamine: 231 Hz ($\underline{CH_2}Ph$, singlet), 438 Hz (Ph, singlet).

The residue was distilled under vacuum to give a mixture of trans-2-benzylamino-cis-4-t-butylcyclohexanol (95a) and trans-2-benzylamino-trans-5-t-butyl-cyclohexanol (95b) (14.5 g, 70%), b.p. 150-156°/2 mm.

PMR characteristics (DMSO-d_6)

50 Hz (t-Bu, singlet), 222 Hz ($\underline{CH_2}Ph$, singlet), 437 Hz (Ph, singlet).

Isomeric t-butyl and $\underline{CH_2}Ph$ signals could not be differentiated, as was also the same when spectra were recorded in $CDCl_3$ (t-Bu at 51.5 Hz) and CCl_4 (t-Bu at 51 Hz).

Ring Opening Mixture from the Epoxide Mixture (94) and Benzylamine

The epoxide mixture (94) (15.4 g, 0.1 mole) and

benzylamine (10.7 g, 0.1 mole), treated as previously described, produced a fraction I (3 g) (b.p. 81-86°/16 mm), a mixture of the starting materials (shown by PMR), and a fraction II (15 g) (b.p. 140-146°/0.1 mm), a mixture of *trans*-2-benzylamino-*cis*-4-butylcyclohexanol (**95a**) and *trans*-2-benzylamino-*trans*-5-*t*-butylcyclohexanol (**95b**). PMR characteristics of fraction II (CCl_4):

51 Hz (*t*-Bu), 222 Hz ($\underline{CH}_2$Ph), 431 Hz (Ph)

The hydrochloride of fraction II was prepared by treating it with ethanol-HCl and evaporating the solvent. PMR characteristics of the total hydrochloride ($CDCl_3$):

50 and 52.5 Hz (*t*-Bu, two singlets of equal intensity), 249 Hz ($\underline{CH}_2$Ph, broad signal), 449 Hz (Ph, multiplet).

The total hydrochloride mixture was debenzylated and treated with aqueous sodium hydroxide. The free amino alcohols were N-tosylated by tosyl chloride to afford the N-tosyl derivatives (detailed procedure see later).

PMR characteristics of the total tosylates (DMSO-d_6) showed two *t*-butyl singlets at 43 Hz and 48 Hz.

trans-2-Benzylamino-*cis*-4-*t*-butylcyclohexanol Hydrochloride (**96a**)

The total ring opened mixture (**95**) (26.1 g, 0.1 mole derived from the 4-*t*-butylcyclohexene oxide (**79**), was

treated with ethanol-HCl and the hydrochlorides of this mixture (96) were obtained as a viscous liquid after evaporation of the solvent. No solid was isolated when ethanol-ether, ether or petroleum-ether was used as solvent. White needles were finally crystallized from n-hexane, m.p. 150-160°.

PMR characteristics ($CDCl_3$)

50 Hz (t-Bu), 52.5 Hz (t-Bu), 249 Hz (CH_2Ph, broad signal), 449 Hz (Ph, multiplet).

The two t-butyl signlets were of equal intensity. PMR characteristics in D_2O showed a singlet at 50 Hz for the t-butyl groups of the two isomers.

Fractional recrystallization of the hydrochloride mixture from ethanol-ether gave white hexagonals of the pure trans-2-benzyl-amino-cis-4-t-butylcyclohexanol hydrochloride (96a) (10 g, 34%), m.p. 175-176°.

PMR characteristics ($CDCl_3$)

50 Hz (t-Bu), 183 Hz (OH, singlet; overlapping with C-2 methine multiplet), 249 Hz (CH_2Ph, broad; the C-1 methine signal was obscured by this resonance peak), 450 Hz (Ph, multiplet).

Anal. Calcd. for $C_{17}H_{28}ClNO$: C, 68.55; H, 9.48.

Found: C, 68.41; H, 9.43.

cis-4-t-butyl-trans-2-tosylamidocyclohexanol (81a)

A crude mixture (95) of benzylaminocyclohexanols

(26 g, 0.1 mole) and 10% Pd/C (2.6 g) in absolute alcohol (50 ml) were hydrogenated under atmospheric pressure and the hydrogenation was stopped after the theoretical amount of hydrogen had been absorbed. The Pd/C was removed by filtration and the solvent evaporated affording a mixture of the primary aminoalcohols (74a and 80) (17 g, 99%). The PMR spectra of this mixture in $CDCl_3$ or DMSO-d_6 could not be used to differentiate the *t*-butyl signal of each isomer, the *t*-butyl signals of two isomers collapsing into one sharp singlet (52 Hz in $CDCl_3$ and 49 Hz in DMSO-d_6).

The mixture of the primary aminoalcohols (17 g, 0.1 mole) was dissolved in benzene (80 ml) and the solution stirred for one hour with a solution of tosyl chloride (21 g, 0.11 mole) in benzene (80 ml) and aqueous 10% NaOH (60 ml). The mixture of N-tosyl derivatives (81a and 81b) which separated in crystalline form was collected, washed with water and a few ml of alcohol. Yield, 30 g (94%), m.p. 165-170°.

PMR characteristics (DMSO-d_6):

43 Hz (*t*-Bu, singlet), 48 Hz (*t*-Bu, singlet), 142 Hz (*Me*Ph, singlet), 454 Hz (Ph, multiplet).

Fractional crystallization of this mixture from ethanol yielded the pure title compound (81a) as lustrous prisms (10 g, 34%), m.p. 191° (Sicher *et al.*, 1961, reported 192-193°).

PMR characteristics (DMSO-d_6):

43 Hz (t-Bu), 141 Hz (MePh), 454 Hz (Ph); two methine proton multiplets overlapping each other in the range 180-215 Hz.

trans-2-amino-cis-4-t-butylcyclohexanol (74a)

a) Sodium (2.0 g, 0.08 mole) was added to a suspension of finely ground cis-4-t-butyl-trans-2-tosylamidocyclohexanol (5.7 g, 0.016 mole) in commercial liquid ammonia (120 ml), in portions during 15 minutes.

After sodium (1.5 g) had been added the color of the solution remained permanently blue. On complete addition of sodium, stirring was continued for another hour, a small amount of ethanol carefully added to decompose the unreacted sodium, and the ammonia then allowed to evaporate. To the mixture was added a few ml. of water and the mixture extracted with ether; the combine extracts were extracted with hydrochloric acid (1:1), the acid extracts shaken with ether and made alkaline with concentrated aqueous sodium hydroxide. The liberated base was dissolved in ether, the ethereal solution dried, the ether evaporated and the residue (74a) (2.2 g, 80%) recrystallized from ethyl acetate-petroleum ether, m.p. 108-109° (Sicher *et al.*, 1961, reported 108.5-109.5°). It gave a hydrochloride, m.p. 237-238° from ethanol-ether (Sicher *et al.*, 1964, reported 239-240°).

PMR characteristics ($CDCl_3$):

52 Hz (t-Bu), 183 Hz (C-2 proton, multiplet with W_H = 9.5 Hz), 218 Hz (C-1 proton, multiplet with W_H = 5 Hz).

b) The pure benzylaminoalcohol hydrochloride (96a) (3 g, 0.01 mole) and 10% Pd/C (0.3 g) in absolute alcohol (10 ml) was hydrogenated under atmospheric pressure until the theoretical amount of hydrogen had been absorbed. The Pd/C was removed and the alcohol was distilled, thus affording the hydrochloride of the title compound (74a) (1.9 g, 95%). The solid was recrystallized from ethanol-ether, m.p. 236-238°, undepressed by the hydrochloride obtained in procedure a).

The hydrochloride was treated with excess 10% aqueous sodium hydroxide and the liberated free base was extracted with ether. The solvent of the dried (Na_2SO_4) ether extracts was evaporated and the residue (74a) crystallized from ethyl acetate-petroleum ether, m.p. 107-109°, undepressed by the free aminoalcohol (74a) derived from pathway a). The N-tosyl derivative of the free aminoalcohol (74a) was prepared as previously described, m.p. 190-192°, mixed m.p. with (81a) 190-192°.

trans-2-Dimethylamino-cis-t-butylcyclohexanol (75a)

A mixture of the aminoalcohol (74a) (0.85 g, 0.005 mole), 40% formaldehyde (6 ml) and 88% formic acid (4 g)

was heated to boiling for 24 hours. The mixture was acidified with concentrated hydrochloric acid and evaporated to dryness. The residue was treated with excess 10% sodium hydroxide and extracted with ether. The solvent of the dried (Na_2SO_4) extract was removed to afford the title compound (0.6 g, 60%). The product was not characterized analytically but its spectroscopic characteristics showed it to be the required material.

IR spectrum:

ν_{max}: 3400 cm^{-1} (OH), 2820 and 2780 cm^{-1} (NCH); absence of ν_{NH} at 3280 and 3175 cm^{-1}.

PMR characteristics ($CDCl_3$)

52 Hz (t-Bu), 134.5 Hz (NMe_2), 235 Hz (C-1 proton, multiplet with W_H = 9.5 Hz); the C-2 proton signal was obscured by the NMe_2 resonance.

trans-2-Dimethylamino-trans-4-t-butylcyclohexyl Acetate Hydrochloride (99)

A benzene solution of the crude dimethylaminoalcohol (75a) (1.0 g, 0.005 mole) and acetyl chloride (1.2 g, 0.0015 mole) was heated under reflux for 2 hours when the solid title compound (1.0 g, 72%) was obtained. Recrystallization of this solid from ethanol-ether gave white prisms, m.p. 183-184°.

IR spectrum:

ν_{max}: 3510-3440 cm^{-1} (overtone of $\nu_{C=O}$, m), 2600-

2480 cm^{-1} ($\overset{+}{\mathrm{N}}\mathrm{H}$), 1750 cm^{-1} (CO).

Anal. Calcd. for $C_{14}H_{28}ClNO_2$: C, 60.52; H, 10.16.

Found: C, 60.42; H, 10.08.

Pyridinium Hydrobromide Perbromate:

Pyridine (30 ml) was mixed with 48% hydrobromic acid (60 ml). To this solution was added bromine (50 g) gradually with swirling and cooling. The red precipitate which formed was collected, washed with acetic acid and recrystallized from acetic acid (200 ml) to give red needles (66 g), m.p. 132-133° (Djerassi and Scholz, 1948, reported 134°).

trans- and cis-2-Bromo-4-t-Butylcyclohexanone (100 and 102)

To a solution of t-butylcyclohexanone (12.3 g, 0.08 mole) in a mixture (350 ml) of equal volumes of chloroform and acetic acid was added pyridinium hydrobromide perbromate (26 g, 0.08 mole) portionwise over 20 minutes while stirring. Immediate loss of red color was noted with the addition of each portion. The mixture was warmed on a steam bath for 1 hour, then poured into 160 ml of petroleum ether and water (1 litre) containing 0.5% sodium sulfite. The organic layer was separated and the aqueous layer extracted with 2 additional portions of petroleum ether. The organic layers were combined, washed with water and saturated NaCl solution, and dried (Na_2SO_4).

Removal of the solvent afforded a pale yellow liquid (18 g, 97%) which was further distilled to give a colorless liquid (14 g, 80%), b.p. 70-85°/0.5 mm. The PMR spectrum of the total distillate showed two broad methine multiplets, one centered at 255 Hz and the other at 272 Hz. A broad carbonyl peak centered at 1725 cm^{-1} appeared in its IR spectrum (thin film).

The distillate was kept in the refrigerator when it completely solidified. When the solid was allowed to stand at room temperature some of it liquified. The residual solid was collected by suction. The filtrate was cooled again. The solidification and room temperature melting procedure repeated several times. The combined residual solids of the cis bromo compound (102) (4 g, 26% overall yield) were recrystallized from n-hexane giving a product, m.p. 66-68° (Allinger and Allinger, 1958, reported 67-68.2°).

IR spectrum:

ν_{max}: 1740 cm^{-1} (CO) (Allinger and Allinger, 1958, reported 1748 cm^{-1} when CCl_4 solution was used).

PMR characteristics (CCl_4)

57 Hz (t-Bu), 272 Hz (axial 2-H, W_H = 18 Hz) (Garbisch, 1964, reported W_H = 17.9 Hz).

The filtrate of the trans bromo isomer (100) (9.7 g, 52%) was obtained after 4 operations of the solidification and melting procedure and its PMR spectrum (CCl_4)

showed that a trace of the cis isomer (102) still remained. This material was used for further reactions.

IR spectrum:

ν_{max}: 1720 cm^{-1} (CO) (Allinger and Allinger, 1958, reported 1724 cm^{-1} when it was dissolved in CCl_4).

PMR characteristics (CCl_4):

56.5 Hz (t-Bu), 255 Hz (equatorial α-H, W_H = 6.5 Hz) (Garbisch, 1964, reported W_H = 5.6 Hz), 272 Hz (axial α-H, very weak in intensity).

cis-2-Benzylamino-4-t-butylcyclohexanone Hydrochloride (103)

Benzylamine (3.0 g, 0.028 mole) was added to the trans bromo isomer (100) (3.4 g, 0.014 mole) in ethanol (20 ml) when the solution turned to a purple color with evolution of heat. The purple solution was then heated to reflux under a nitrogen atmosphere until the color faded (about 3 hours). At this moment, crystals started to settle out. The refluxed solution was cooled and ether added to complete precipitation. The crystals of benzylamine hydrobromide were collected, m.p. 220° (Heilbron, 1965, reported 204°) mixed m.p. with benzylamine hydrobromide (prepared by treating benzylamine with hydrogen bromide, m.p. 211-222°) 219-221°. The solvent of the filtrate was evaporated, giving a residue (4.5 g). The residue was treated with ethanol-HCl and the benzylamine

hydrochloride, m.p. 258-260° (Merck Index, 1968, reported 253°), mixed m.p. with benzylamine hydrochloride (prepared by treating benzylamine with ethanol-HCl) 258-261°, which formed was collected. The filtrate was heated under reflux for 30 minutes. Anhydrous ether was then added and the solution cooled when the title compound (0.22 g, 5%) separated as white prisms, m.p. 208-210°.

IR spectrum:

ν_{max}: 2725-2645 cm^{-1} ($\overset{+}{\mathrm{NH}}$), 1730 cm^{-1} (CO)

PMR characteristics (CDCl$_3$):

52 Hz (*t*-Bu), 218 Hz (α-H), W_H = 20 Hz), 255 Hz ($\underline{\mathrm{CH_2}}$Ph, W_H = 10.5 Hz), 445 Hz (Ph, multiplet).

Anal. Calcd. for $C_{17}H_{26}ClNO$: C, 69.01; H, 8.85.

Found: C, 67.19; H, 8.26.

This analysis is unsatisfactory, hence the product is impure.

trans-2-Dimethylamino-4-*t*-butylcyclohexanone Hydrochloride (**104**)

A stream of nitrogen was passed for 0.5 hour through an ethanol solution (10 ml) of the *trans* bromo isomer (**100**) (5 g, 0.02 mole) in a three-necked flask, to which was attached a dry-ice condenser, cooled in a dry ice-acetone bath. The nitrogen source was removed and anhydrous dimethylamine (20 ml) (at 0°) added. The dry ice-acetone

bath was removed and the mixture allowed to reflux for 7 hours while stirring. The excess dimethylamine was evaporated under diminished pressure and ether added. Crystals of dimethylamine hydrobromide (its IR spectrum showed no $\nu_{C=O}$ absorption) which separated were removed by filtration and a few ml of ethanol-HCl added to the filtrate to bring about precipitation of the residual unreacted dimethylamine as hydrochloride (this crystallized out very rapidly). The filtrate (after removal of the hydrochloride) was heated under reflux with ethanol-HCl for 0.5 hour and ether added to this solution. White crystals of the title compound (3.5 g, 70%) were obtained, 180-183°.

IR spectrum:

ν_{max}: 2530-2300 cm^{-1} ($\overset{+}{N}H$), 1730 cm^{-1} (CO)

PMR characteristics (D_2O):

57 Hz (t-Bu), 172 Hz (NMe_2), 254 Hz (α-H, W_H = 20 Hz).

Anal. Calcd. for $C_{12}H_{23}ClNO$: C, 61.64; H, 10.35.

Found: C, 58.96; H, 10.90.

The analysis is unsatisfactory, hence the material is impure.

When the reaction was carried out as above except without using ethanol as solvent, no reaction took place, the starting material (shown by PMR) being recovered and no dimethylamine hydrobromide formed.

Isomeric Reduced Products of the Ketone Hydrochloride (104)

The crude aminoketone hydrochloride (104) (1.5 g, 0.006 mole), m.p. 167-171° (the presence of $\nu_{C=O}$ peak was shown by IR) was dissolved in absolute alcohol (20 ml) and the solution subjected to atmospheric hydrogenation over platinum oxide (0.4 g). After 7 days shaking with hydrogen more than the theoretical amount of hydrogen had been absorbed (this could have been due to leakage), the catalyst was removed by filtration, and the methanol was distilled affording a mixture of the desired alcohols and unreacted ketone. The IR spectrum of the mixture (in Nujol) showed a medium $\nu_{C=O}$ band at 1730 cm^{-1} and a strong ν_{OH} peak at 3310 cm^{-1}. Fractional recrystallization of this mixture from ethanol-ether gave the reduced alcohols (1 g, 67%), m.p. 230-232°.

IR spectrum:

ν_{max}: 3395 and 3310 cm^{-1} (OH), 2700 cm^{-1} ($\overset{+}{N}H$), (no $\nu_{C=O}$ at 1730 cm^{-1}).

PMR characteristics (D_2O)

50 Hz (t-Bu), 54 Hz (t-Bu), 174 Hz (NMe_2), 261 Hz (C-1 methine proton, W_H = 10 Hz); C-2 methine proton signal was obscured by NMe_2 singlet.

Anal. Calcd. for $C_{12}H_{26}ClNO$: C, 61.12; H, 11.11.

Found: C, 61.39; H, 11.12.

It is evident from the presence of two *t*-butyl singlets in its PMR spectrum that the product was a mixture of *cis*-2-dimethylamino-*cis*-4-5-butylcyclohexanol hydrochloride (**105a**) and *trans*-2-dimethylamino-*trans*-4-*t*-butylcyclohexanol hydrochloride (**105b**). The intensity of the singlet at 54 Hz was twice as that at 50 Hz.

trans-2-Carbomethoxyamino-*cis*-4-*t*-butylcyclohexyl Iodide (**110a**)

To a cold solution (-40°C) of 4-*t*-butylcyclohexene (**78**) (27.7 g, 0.2 mole) in anhydrous ether (500 ml) was added silver cyanate (47 g, 0.31 mole) and iodine (50.7 g, 0.2 mole) portionwise. The mixture was allowed to warm to room temperature and stirred for 48 hours when it became a yellow green slurry. The inorganic salts were removed by gravimetric filtration.

To the filtrate was added anhydrous methanol (50 ml) and the solution heated under reflux for 6 hours and allowed to stand overnight (the solution was then reddish brown). The solution was washed with 10% aqueous sodium sulfite solution (150 ml) and then with water (100 ml) and finally dried (Na_2SO_4). The ether was removed and the residue was subjected to distillation under water pressure to remove the unreacted cyclohexene (**78**).

PMR characteristics of the residue ($CDCl_3$)

54 Hz (*t*-Bu), 64 Hz (*t*-Bu), 219 Hz (OMe) 221 Hz (OMe), no vinylic signal at 336 Hz.

The pale yellow solid (10 g) which crystallized from the cooled residue was collected; the PMR spectrum of this solid showed a major t-butyl signal at 54 Hz and a very weak t-butyl singlet at 64 Hz. To the filtrate was added a few ml. of methanol when another crop of solid (5 g) separated; the PMR spectrum of this solid was the same as that of the former. The combined crops were recrystallized twice from chloroform-methanol to give a pure isomer of white prisms of the title compound (14 g, 21%), m.p. 154-155°.

IR spectrum:

ν_{max} = 3260 and 3120 cm^{-1} (NH), 1700 cm^{-1} (CO)

PMR characteristics ($CDCl_3$)

54 Hz (t-Bu), 221 Hz (OMe) 246 Hz (C-2 methine proton, multiplet with W_H = 14 Hz), 276 Hz (C-1 methine proton, multiplet with W_H = 7 Hz). 308 Hz (NH, broad signal).

Anal. Calcd. for $C_{12}H_{22}INO_2$: C, 42.49; H, 6.53.

Found: C, 42.18; H, 6.37.

Cyclic Urethane of cis-2-Amino-trans-4-t-butyl-cyclohexanol (111)

The pure acyclic urethane (110a) (5 g, 0.013 mole) was heated in an oil bath at 150° at 0.01 mm for 20 minutes. The yellow residue was recrystallized from ethyl acetate affording white prisms of (111) (2 g, 80%), m.p. 140-142°

(Sicher et al., 1961, reported 145-146°).

IR spectrum:

ν_{max}: 3220 and 3120 cm^{-1} (NH), 1750 cm^{-1} (CO)

PMR characteristics ($CDCl_3$)

52 Hz (t-Bu), 247 Hz (C-2 methine proton, multiplet with W_H = 7 Hz),278 Hz (C-1 methine proton, multiplet with W_H = 14 Hz), 355 Hz (NH).

Anal. Calcd. for $C_{11}H_{19}NO_2$: C, 66.96; H, 9.70.

Found: C, 67.16; 9.62.

cis-2-Amino-trans-4-t-butylcyclohexanol (74c)

A solution of the cyclic urethane (111) (1.3 g, 0.007 mole) in 10% aqueous ethanolic 1N potassium hydroxide (100 ml) was heated under reflux for 12 hours. The ethanol was distilled and the residual aqueous solution extracted with $CHCl_3$. The combined $CHCl_3$ extracts were dried (Na_2SO_4) and the solvent removed yielding (74c) as a white solid (0.9 g, 80%), m.p. 108-111°. The solid when crystallized from benzene-petroleum ether had m.p. 112-113° (Sicher et al, 1961, reported m.p. 112-113°), mixed m.p. with authentic cis-2-amino-5-cis-t-butylcyclohexanol (112) (from Sicher) 85-86°. It gave a hydrochloride m.p. 242-244° (Sicher et al., 1964, reported 249-250°).

PMR characteristics ($CDCl_3$)

51 Hz (t-Bu), 191 Hz (C-2 methine proton, multiplet with W_H = 8 Hz), 211 Hz (C-1 methine proton, multiplet

with W_H = 19 Hz).

Anal. Calcd. for $C_{10}H_{12}NO$: C, 70.12; H, 12.36.

Found: C, C, 70.39; H, 12.23.

cis-2-Dimethylamino-trans-4-t-butylcyclohexanol (75c)

A mixture of the aminoalcohol (74c) (0.51 g, 0.003 mole), 40% formaldehyde (4 ml) and 88% formic acid (2.7 g) was heated under reflux for 24 hours and treated as previously described for making (75a). The pale yellow liquid (0.52 g, 88%) obtained was used without further purification.

PMR characteristics ($CDCl_3$):

52 Hz (t-Bu), 143 Hz (NMe_2), 155 Hz (C-2 methine proton, partially obscured by NMe_2 singlet) 219 Hz (C-1 methine proton, multiplet with W_H = 10 Hz).

cis-2-Dimethylamino-trans-4-t-butylcyclohexyl Acetate Hydrochloride (113)

A benzene solution of the dimethylaminoalcohol (75c) (0.39 g, 0.0015 mole) and acetyl chloride (0.314 g, 0.004 mole) was heated under reflux for 2 hours, white crystals (0.4 g, 95%) being collected. Upon recrystallization from ethanol-ether these melted at 140-142°.

IR spectrum:

ν_{max}: 3500 and 3440 cm^{-1} (overtone of $\nu_{C=O}$, m), 2660-2470 cm^{-1} ($\overset{+}{N}H$), 1745 cm^{-1} (CO).

Anal. Calcd. for $C_{14}H_{28}ClNO_2$: C, 60.52; H, 10.16.

Found: C, 60.52; H, 10.16.

Attempt to Prepare 2-Carboxyl-4-*t*-Butylcyclohexanone (87)

A small piece of potassium metal was added to stirred liquid ammonia (250 ml) in a 500 ml three necked flask equipped with a mechanical stirrer and a dry ice condenser, to which a $CaCl_2$ drying tube was connected. After the appearance of a blue color, a few crystals of ferric nitrate hydrate were added to discharge the coloration, followed by another small piece of ptassium. This procedure was continued until potassium (4.5 g, 0.115 g atom) had been added.

A solution of triphenylmethane (28.1 g, 0.115 mole) in anhydrous ether (150 ml) was added to the stirred potassium amide (0.115 mole) as rapidly as the ammonia was efficiently condensed. The mixture acquired an orange color. After one hour, the dry ice in the condenser was replaced by crushed ice. The reaction mixture was then allowed to rise to room temperature and finally heated until no ammonia was evolved from the condenser, sufficient anhydrous ether being added gradually so that the volume of the mixture remained approximately 300 ml. The potassium triphenyl methylide reagent was obtained as blood red suspension in ether.

The thus formed suspension was treated with a 50% ethereal solution of 4-*t*-butylcyclohexanone; the temperature was maintained at 0-10° and the addition was continued

until the solution decolorized; this occurred after the ketone (15 g) had been introduced.

The reaction mixture was then transferred under nitrogen into a flask containing lumps of dry ice (100 g), allowed to stand overnight while cooled by an ice bath, and then shaken with a cold (at -5°) 10% sodium hydroxide solution (100 ml). The aqueous alkaline solution was extracted twice with ether and then under cooling (-5° to 5°) acidified with 15% aqueous hydrochloric acid (at -5°).

A dark brown, viscous oil separated and taken up in ether; the aqueous solution was extracted twice with ether. The combined ethereal extracts were evaporated to dryness and kept in a refrigerator when a dark brown lump (8 g) formed. The product was dried in a vacuum desiccator; colorless prisms emerged on the surface of the lump. The prisms (0.5 g), m.p. 48-50°, mixed m.p. with the starting material 48-49°, were collected and their IR spectrum was superimposable with that of 4-t-butylcyclohexanone. The lump was distilled, and the distillate (5 g), b.p. 105-106°/15 mm, m.p. 48-49°, mixed m.p. with authentic 4-t-butylcyclohexanone 48-49°.

This process was tried once only. The recovery of the starting material is possibly due to decarboxylation of the carboxylated product when it was treated with the acid.

2-Carbethoxy-4-t-butylcyclohexanone (14)

A 250 ml three necked flask equipped with a magnetic stirrer was fitted with a 100 ml dropping funnel and a condenser, the top of which was connected to a mercury trap to prevent the entrance of air during the reaction and for the detection of gas evolution. 61% sodium hydride dispersion in mineral oil (12 g, 0.3 mole) was added to the flask and washed four times with benzene (50 ml). The benzene was removed with a pipette after the sodium hydride had settled.

After most of the mineral oil had been removed, benzene (120 ml) was added to the NaH, followed by diethyl carbonate (23.6 g, 0.2 mole). This mixture was heated under reflux, and a solution of 4-t-butylcyclohexanone (15.4, 0.1 mole) in benzene (50 ml) was added dropwise over a period of 4 hours. After the addition was complete, this mixture was kept at the reflux temperature until the evolution of hydrogen ceased (ca. 1.5 hours). When the reaction mixture had cooled to room temperature, glacial acetic acid (20 ml) was added dropwise, followed by ice-cold water (100 ml), and the stirring was continued until all the material had gone into the solution. The benzene layer was separated, and the aqueous layer was extracted three times with benzene (50 ml). The combined benzene extracts were washed with cold water (50 ml) three times.

The benzene and the excess diethyl carbonate were removed under water-pump pressure by gentle heating, and the residual material distilled. The fraction (b.p. 90-115°/1 mm) was collected. Redistillation gave the title compound (16 g, 71%), b.p. 99°/0.8 mm.

IR spectrum:

ν_{max}: 1745 and 1725 cm^{-1} (CO of the keto form), 1655 and 1615 cm^{-1} (CO of the enol form).

PMR characteristics (CCl_4)

55 Hz (t-Bu), 178 Hz ($\underline{CH_3}$ CH_2O, triplet), 250 Hz (CH_3 $\underline{CH_2}O$, quartet); the ethyl signal of CH_3CH_2O varied from batch to batch probably because of the change in isomeric proportion.

Anal. Calcd. for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80

Found: C, 69.24; H, 10.03.

cis-5-t-Butyl-trans-2-hydroxycyclohexanecarboxylic Acid (85)

A solution of the ester (114) (22.6 g, 0.1 mole) and sodium borohydride (1.89 g, 0.1 mole) in absolute alcohol (250 ml) was stirred for 4 hours at 0° and then acidified to pH 4-6 by addition of dilute hydrochloric acid. After the resulting mixture had been concentrated, the residue was extracted with ether and the ethereal extract was dried (Na_2SO_4) and evaporated to dryness, thus giving the reduced compound (115) (21 g, 92%), which

consisted of a mixture of stereoisomers of ethyl 5-t-butyl-2-hydroxycyclohexanecarboxylate. The sample used for analysis distilled at 86°/0.05 mm.

Anal. Calcd. for $C_{13}H_{24}O_3$: C, 68.38; H, 10.58.

Found: C, 68.41; H, 10.34.

The crude reduced product (115) (12 g, 0.06 mole) was dissolved in 5% sodium methoxide in methanol (60 ml) and the mixture allowed to stand for 12 hours, then refluxed for 2 hours and treated with 50% aqueous sodium hydroxide solution (containing about 1 g of the hydroxide); the last treatment instantly brought about crystallization of the sodium salt. The crystals were collected, dissolved in hot water (50 ml) and acidified with conc. hydrochloric acid. The acid separated as an oil which crystallized upon cooling; it was extracted with ether and the dried (Na_2SO_4) ether extract evaporated to give a crystalline residue (7.5 g), which on crystallization from acetone yielded the title compound (7 g, 60%), m.p. 144-145° Sicher et al., 1961, reported 146-147°). The methanol of the filtrate (from which the sodium salt separated) was taken off and the semisolid residue thus obtained was treated as described for the crystals. The acid, in this case, failed to crystallize from acetone.

Diazomethane in Ether

Ethanol (95%, 25 ml) was added to a solution of potassium hydroxide (5 g) in water (8 ml) in a 100 ml

distilling flask fitted with a dropping funnel and an efficient condenser set downward for distillation. The condenser was connected to two receiving flasks in series, the second of which contained ether (20-30 ml). The inlet tube of the second receiver dipped below the surface of the ether, and both receivers were cooled to 0°.

The flask containing the alkali solution was heated in water bath to 65°, and a solution of N-methyl-N-nitroso-p-toluenesulfonamide (diazald, Aldrich) (21.5 g 0.1 mole) in ether (about 200 ml) was added through the dropping funnel during 1 hour. When the dropping funnel was empty, more ether (40 ml) was added slowly and the distillation was continued until the distilling ether was colorless. The combined ethereal distillate contained about 3 g of diazomethane (this yield is given by Aldrich).

Methyl cis-5-t-Butyl-trans-2-hydroxycyclohexanecarboxylate (89)

The free acid (85) (4.5 g, 0.023 mole) was directly esterified by addition of a small excess of the ethereal diazomethane prepared from diazald (10 g). After about 10 minutes the resulting solution was treated with a few drops of glacial acetic acid and dried (Na_2SO_4). The solvent was distilled leaving the title ester (3.5 g, 63%) which, upon recrystallization from petroleum ether,

melted at 76-77.5° (Sicher *et al.*, 1961, reported 79.80°). The crude sample was used for conversion to the hydrazide (83).

cis-5-*t*-Butyl-*trans*-2-hydroxycyclohexanecarboxylic Acid Hydrazide (83)

The methyl ester (89) (2.1 g, 0.01 mole) in ethanol (1 ml) was heated with 95% hydrazine (0.76 g, 0.02 mole) on the water bath for one hour; on cooling the hydrazide (83) (1.5 g) separated, m.p. 178-179° (Sicher *et al.*, 1961, reported 177-178°). The filtrate was evaporated to dryness and the residue was recrystallized from ethanol to afford another crop of the title compound (0.5 g). The total yield was 2 g (93%).

Cyclic Urethane of *trans*-2-Amino-*trans*-4-*t*-butylcyclohexanol (84)

A solution of the hydrazide (83) (1.1 g, 0.005 mole) in 1.1% aqueous hydrochloric acid (20 ml) was treated under efficient stirring with a solution of sodium nitrite (0.4 g, 0.006 mole) in water (8 ml) maintaining the temperature at 0-5° by external cooling; the stirring was continued for further hour after the addition. The mixture was extracted with ether and the combined extracts dried (Na_2SO_4). Absolute ethanol (10 ml) was added to the filtered ethereal solution and the ether removed under

diminished pressure without heating; the residual ethanolic solution was then refluxed for one hour. Evaporation of the ethanol yielded a solid residue of the cyclic urethane (0.8 g 81%), m.p. 112-115° (Sicher *et al.*, 1961, reported 124-125°). This crude product was used for hydrolysis.

trans-2-Amino-*trans*-4-*t*-butylcyclohexanol (*74d*)

A solution of the cyclic urethane (*84*) (0.7 g, 0.004 mole) in 1N KOH in water-ethanol (10:1) (10 ml) was heated under reflux for 10 hours. The ethanol was distilled and the residue extracted with ether. The ethereal extracts were dried (Na_2SO_4), the solvent distilled and the residue upon recrystallization from ethyl acetate-petroleum ether afforded the aminoalcohol (*74d*) (0.5 g, 82%), m.p. 92-94° (Sicher *et al.*, 1961, reported 94.5-95.5°).

PMR characteristics ($CDCl_3$):

52 Hz (*t*-Bu), 147 Hz (OH, overlapping with C-2 methine multiplet), 182 Hz (C-1 methine proton, multiplet with W_H = 20 Hz).

iv) SYNTHESIS OF MORPHOLINE DERIVATIVES

N-Methylmorpholine

A mixture of 40% formaldehyde in water (112 ml, 1.3 moles) and 88% formic acid (46 g, 1.3 moles) was added dropwise to morpholine (87 g, 1 mole) while cooled with an ice-bath. The addition took about 1 hour and the mixture was then refluxed for 5 hours.

20% Hydrochloric acid was added to the refluxed solution to acidify the base and the solution was evaporated to dryness under reduced pressure. The residue was treated with excess 10% aqueous NaOH, extracted with ether and dried (Na_2SO_4). The solvent was evaporated and the residue distilled to give N-methylmorpholine as a colorless liquid (75 g, 74%), b.p. 110-111° (Knorr, 1889, reported 116-117°/764 mm). It gave a hydrochloride, m.p. 205-206° from ethanol-ether (Knorr, 1889, reported 205°).

N,N-Dimethylmorpholinium Iodide (117)

A mixture of N-methylmorpholine (10 g, 0.1 mole) and methyl iodide (2.8 g, 0.2 mole) in methanol was heated for two hours. To this mixture was added anhydrous ether and the product then cooled. The crystalline solid which separated was collected and recrystallized from absolute alcohol to give the title compound as white needles (20 g, 83%), m.p. 246-248° (Knorr and Metthes, 1889, reported 251°).

N-Benzyl-N-methylmorpholinium Bromide (118)

The title compound was prepared in 93% yield in the same manner as that described for making the corresponding methiodide (117); it had m.p. 190-191° from abs. ethanol.

Anal. Calcd. for $C_{12}H_{18}BrNO$: C, 52.94; H, 6.66.
Found: C, 52.97; H, 6.49.

N-Methyl-cis-2,6-dimethylmorpholine Hydrochloride (120a)

Analogous to N-methylation of morpholine, a commercial cis and trans 2,6-dimethylmorpholine mixture (115 g, 1 mole) was treated with 40% formaldehyde (112 ml) and 88% formic acid (78 g) and was then acidified with conc. hydrochloric acid to give a crude mixture of the cis and trans N-methylated hydrochlorides (132 g, 80%). Fractional crystallization of the mixture from ethanol-ether gave the pure N-methyl-cis-2,6-dimethylmorpholine hydrochloride (120a) (106 g, 64%), m.p. 222-223°.

NMR characteristics ($CDCl_3$):

74 Hz (2,6-Me, doublet with J = 6.5 Hz), 171.5 Hz (H$\overset{+}{N}$Me, doublet with J = 5 Hz), 256 (methine protons, multiplet).

Anal. Calcd. for $C_7H_{16}ClNO$: C, 50.75; H, 9.73.
Found: C, 50.85; H, 9.63.

The mother liquid was recrystallized several times and a mixture richer in the trans isomer (120b) was

obtained, but the pure *trans* isomer could not be isolated.

PMR characteristics ($CDCl_3$) (only signals of *trans* isomers are given):

71 Hz (equational Me, doublet with J = 6 Hz), 99.5 Hz (axial Me, doublet with J = 7 Hz), 174 Hz ($H\overset{+}{N}\underline{Me}$ doublet with J = 5 Hz).

N-Methyl-*cis*-2,6-dimethylmorpholine (121)

The pure *cis* hydrochloride (120a) (16.5 g, 0.1 mole) was treated with excess 10% aqueous sodium hydroxide and extracted with ether. The combined ether extracts were dried (Na_2SO_4) and the solvent evaporated. Distillation of the residue gave the base (121) as a colorless liquid (11.5 g, 90%), b.p. 132-134°. The sample was not analysed.

PMR characteristics ($CDCl_3$):

69 Hz (2,6-Me, doublet with J = 6.5 Hz), 134 Hz (NMe), 221 Hz (methine protons, multiplet).

N,N-Dimethyl-*cis*-,6-dimethylmorpholinium Iodide (122)

The base (121) with methyl iodide (see preparation of 117) gave the title compound, m.p. 230.5-231.5°, in 95% yield.

PMR characteristics (D_2O):

76 Hz (2,6-Me, doublet with J = 6 Hz), 197 Hz

(NMe), 256 Hz (methine protons, broad signal).
Anal. Calcd. for $C_8H_{18}ONI$: C, 35.42; H, 6.69.
Found: C, 35.66; H, 6.78.

N-Benzyl-N-methyl-cis-2,6-dimethylmorpholinium Chloride (123)

A mixture of the cis isomer (121) (6.5 g, 0.05 mole) and benzyl chloride (6.3 g, 0.05 mole) in absolute alcohol (30 ml) was heated to reflux for 10 hours. The alcohol was taken off under diminished pressure affording white crystals (12.5 g, 98%) of the quaternary α and β mixture (123).

PMR characteristics (D_2O) (DSS as standard):

76 Hz (2,6-Me, doublet with J = 6.5 Hz), 79 Hz (2,6-Me, doublet with J = 6 Hz; slightly more intense than signal at 76 Hz), 184 Hz (NMe), 190 Hz (NMe, slightly less intense than signal at 184 Hz), 276 Hz (CH_2Ph), 286 Hz ($\underline{CH_2}Ph$, slightly more intense than signal at 276 Hz).

Upon fractional recrystallization from ethanol-ether the crude product yielded the α-isomer of the title compound (3 g, 23%), m.p. 264-265°.

PMR characteristics (D_2O) (DSS as standard):

79 Hz (2,6-Me, doublet with J = 6.5 Hz), 184 Hz (NMe), 286 Hz (CH_2Ph).

Anal. Calcd. for $C_{14}H_{22}ClNO$: C, 65.77; H, 8.67.

Found: C, 65.73; H, 8.82.

Evaporation of the mother liquid and crystallization of the residue thus obtained from ethanol-acetone-

ether gave the β-isomer of the title compound (1 g, 8%), m.p. 236-237°.

PMR characteristics (D_2O) (DSS as standard):

76 Hz (2,6-Me, doublet with J = 6.5 Hz), 190 Hz (NMe), 276 Hz ($\underline{CH_2}Ph$).

Anal. Calcd. for $C_{14}H_{22}ClNO$: C, 65.77; H, 8.67.

Found: C, 65.47; H, 9.00.

N,N-Dimethylcyclohexylamine

A mixture of cyclohexylamine (20 g, 0.2 mole), 40% formaldehyde (33 ml, 0.44 mole), 88% formic acid (30 g, 0.44 mole) and water (40 ml) was refluxed for 6 hours. The solution was made basic with sodium hydroxide and extracted with ether, and the extract was dried (Na_2SO_4). The ether was evaporated and the residue distilled, yielding a colorless oil of the title compound (12 g, 50%), b.p. 154-160° (Veidělek *et al*., 1960, reported 160°). It gave a hydrochloride, m.p. 224-226° from ethanol-ether (Veidělek *et al*., 1960, reported 215-216°).

Cyclohexyltrimethylammonium iodide (**132**)

An ethanol solution of N,N-dimethylcyclohexylamine (3 g, 0.02 mole) and methyl iodide (5 g, 0.04 mole) was warmed for 10 minutes and then cooled. The white crystals (5 g, 78%) were collected and recrystallized from ethanol, m.p. 276-278° (Veidělek *et al*., 1960, reported 264-265°).

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